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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 265/30, 211/70, C07C 229/00
C07C 233/00

A1

(11) International Publication Number: WO 92/12140

(43) International Publication Date: 23 July 1992 (23.07.92)

(21) International Application Number: PCT/US91/09801

(22) International Filing Date: 27 December 1991 (27.12.91)

(30) Priority data:
635,287 28 December 1990 (28.12.90) US

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU ,SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

(54) Title: PEPTIDES KETOAMIDES, KETOACIDS, AND KETOESTERS

(57) Abstract

Peptides ketoamides, ketoacids, and ketoesters, their use in inhibiting serine proteases and cysteine proteases.

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PEPTIDE KETOAMIDES, KETOACIDS, AND KETOESTERS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a novel class of peptide ketoesters, peptide ketoacids, and ketoamides useful for selectively inhibiting serine proteases, selectively inhibiting cysteine proteases, generally inhibiting all serine proteases, and generally inhibiting all cysteine proteases. Serine proteases and cysteine proteases are involved in numerous disease states and inhibitors for these enzymes can be used therapeutically for the treatment of diseases involving serine proteases or cysteine proteases. We have discovered that peptide α-ketoesters, peptide α-ketoacids, and α-ketoamides can be constructed to inhibit selectively individual serine or cysteine proteases or groups of serine or cysteine proteases. We have found that peptide ketoesters, ketoacids, and ketoamides which contain hydrophobic aromatic amino acid residues in the P_1 site are potent inhibitors of chymases and chymotrypsin-like enzymes. Ketoesters, acids, and amides containing small hydrophobic amino acid residues at the P_1 position are good inhibitors of elastases. Inhibitors of elastases and chymases are useful as anti-inflammatory agents. We have found that peptide ketoesters, amides, and acids which contain cationic amino acid residues such as Arg and Lys in the P_1 site are potent inhibitors of trypsin and blood coagulation enzymes. These inhibitors are thus useful as anticoagulants. Cysteine proteases such as papain, cathepsin B, and calpain I and II are also inhibited by ketoesters. Ketoesters, acids, and amides with aromatic amino acid residues in the P_1 site would be good inhibitors for cathepsin B and papain. Thus, they would have utility as anticancer agents. Ketoesters, ketoacids, and ketoamides with either aromatic amino acid residues or small hydrophobic alkyl amino acid residues at P_1 are good inhibitors of calpain I and II. These inhibitors are useful as neuroprotectants and can be used as therapeutics for the treatment of neurodegeneration.

2. Nomenclature

In discussing the interactions of peptides with serine and cysteine proteases, we have utilized the nomenclature of Schechter and Berger [*Biochem. Biophys. Res. Commun.* 27, 157-162 (1967); incorporated herein by reference]. The individual amino acid residues of a substrate or inhibitor are designated P_1, P_2, etc. and the corresponding subsites of the enzyme are designated S_1, S_2, etc. The scissile bond of the substrate is S_1-S_1'. The primary substrate recognition site of serine proteases is S_1. The most important recognition subsites of cysteine proteases are S_1 and S_2.

Amino acid residues and blocking groups are designated using standard abbreviations [see J. Biol. Chem. 260, 14-42 (1985) for nomenclature rules; incorporated herein by reference]. An amino acid residue (AA) in a peptide or inhibitor structure refers to the part structure -NH-CHR$_1$-CO-, where R_1 is the side chain of the amino acid residue AA. A peptide α-ketoester residue would be designated -AA-CO-OR which represents the part structure -NH-CHR$_1$-CO-CO-OR. Thus, the ethyl ketoester derived from benzoyl alanine would be

designated Bz-Ala-CO-OEt which represents C_6H_5CO-NH-CHMe-CO-CO-OEt. Likewise, peptide ketoacid residues and peptide ketoamide residues would be designated -AA-CO-OH and -AA-CO-NH-R respectively. Thus, the ethyl keto amide derived from Z-Leu-Phe-OH would be designated Z-Leu-Phe-CO-NH-Et which represents $C_6H_5CH_2OCO$-NH-CH(CH_2CHMe_2)-CO-NH-CH(CH_2Ph)-CO-CO-NH-Et.

3. Description of the Related Art

Serine Proteases. Serine proteases play critical roles in several physiological processes such as digestion, blood coagulation, complement activation, fibrinolysis, viral infection, fertilization, and reproduction. Serine proteases are not only a physiological necessity, but also a potential hazard if they are not controlled. Uncontrolled proteolysis by elastases may cause pancreatitis, emphysema, rheumatoid arthritis, bronchial inflammation and adult respiratory distress syndrome. It has been suggested that a new trypsin-like cellular enzyme (tryptase) is involved in the infection of human immunodeficiency virus type 1 [HIV-1; Hattori et al., *FEBS Letters* 248, pp. 48-52 (1989)], which is a causative agent of acquired immunodeficiency syndrome (AIDS). Plasmin is involved in tumor invasiveness, tissue remodeling, blistering, and clot dissociation. Accordingly, specific and selective inhibitors of these proteases should be potent anticoagulants, anti-inflammtory agents, anti-tumor agents and anti-viral agents useful in the treatment of protease-related diseases [Powers and Harper, *Proteinase Inhibitors*, pp 55-152, Barrett and Salvesen, eds., Elsevier, (1986); incorporated herein by reference]. *In vitro* proteolysis by chymotrypsin, trypsin or the elastase family is a serious problem in the production, purification, isolation, transport or storage of peptides and proteins.

Elastase inhibitors are anti-inflammatory agents which can be used to treat elastase-associated inflammation including rheumatoid arthritis and emphysema. Although the naturally occurring protease inhibitor, α1-protease inhibitor (α1-PI) has been used to treat patients with emphysema, this protein inhibitor is not widely used clinically due to the high dosage needed for treatment and the difficulty of producing large quantities. Therefore small molecular weight elastase inhibitors are needed for therapy. Other low molecular weight elastase inhibitors have utility for the treatment of emphysema and inflammation (see: 1-carpapenem-3-carboxylic esters as anti-inflammatory agents, U.S. Patent 4,493,839; N-carboxyl-thienamycin esters and analogs thereof as anti-inflammatory agents, U.S. Patent 4,495,197; incorporated herein by reference).

Anticoagulants and antithrombotic drugs are used in a variety of thrombotic disorders. The 1990 Physician's Desk Reference lists several anticoagulant drugs (heparin, protamine sulfate and warfarin), a few antiplatelet drugs (aspirin) and several thrombolytic agents. Heparin and warfarin are commonly used clinically for prevention and treatment of venous thrombosis and pulmonary embolism. Heparin inhibits the blood coagulation activity by accelerating the binding of natural plasma protease inhibitor antithrombin III with coagulation factors, and warfarin acts as a vitamin K antagonist and inhibits the synthesis of coaguation factors. None of the anticoagulant drugs, antithrombotic drugs, fibrinolytic agents and

antiplatelet drugs are highly effective in all clinical situations and many induce side reactions [Von Kaulla, *Burger's Medicinal Chemistry, Part II*, pp 1081-1132, Wolff, ed., (1979); incorporated herein by reference]. Coagulation disorders such as disseminated intravascular coagulation, bleeding complications of medical and surgical procedures and bleeding complications of systemic illness are still difficult to manage [Ingram, Brozovic and Slater, *Bleeding Disorders*, pp 1-413, Blackwell Scientific Publications, (1982); incorporated herein by reference]. In the treatment of patients with coagulation problems, anticoagulant or antithrombotic agents of diverse mechanisms are urgently sought in order to provide better medical care. Inhibitors for the trypsin-like enzymes involved in blood coagulation are useful anticoagulants *in vivo* [see for example: H-D-Phe-Pro-Arg-CH_2Cl, Hanson and Harker, *Proc. Natl. Acad. Sci.* 85, 3184-3188 (1988); 7-Amino-4-chloro-3-(3-isothiureidopropoxy)isocoumarin (ACITIC), Oweida, Ku, Lumsden, Kam, and Powers, *Thrombos. Res.* 58, 191-197 (1990); incorporated herein by reference].

Cysteine Proteases. Cysteine proteases such as calpain use a cysteine residue in their catalytic mechanism in contrast to serine proteases which utilize a serine residue. Cysteine proteases include papain, cathepsin B, calpains, and several viral enzymes. Neural tissues, including brain, are known to possess a large variety of proteases, including at least two calcium stimulated proteases termed calpains. Calpains are present in many tissues in addition to the brain. Calpain I is activated by micromolar concentrations of calcium while calpain II is activated by millimolar concentrations. In the brain, calpain II is the predominant form, but calpain I is found at synaptic endings and is thought to be the form involved in long term potentiation, synaptic plasticity, and cell death. Other Ca^{2+} activated cysteine proteases may exist, and the term "calpain" is used to refer to all Ca^{2+} activated cysteine proteases, including calpain I and calpain II. The terms "calpain I" and "calpain II" are used herein to refer to the micromolar and millimolar activated calpains, respectively, as described above. While calpains degrade a wide variety of protein substrates, cytoskeletal proteins seem to be particularly susceptible to attack. In some cases, the products of the proteolytic digestion of these proteins by calpain are distinctive and persistent over time. Since cytoskeletal proteins are major components of certain types of cells, this provides a simple method of detecting calpain activity in cells and tissues. Thus, calpain activation can be measured indirectly by assaying the proteolysis of the cytoskeletal protein spectrin, which produces a large, distinctive and biologically persistent breakdown product when attacked by calpain [Siman, Baudry, and Lynch, *Proc. Natl. Acad. Sci. USA* 81, 3572-3576 (1984); incorporated herein by reference]. Activation of calpains and/or accumulation of breakdown products of cytoskeletal elements has been observed in neural tissues of mammals exposed to a wide variety of neurodegenerative diseases and conditions. For example, these phenomena have been observed following ischemia in gerbils and rats, following stroke in humans, following administration of the toxins kainate, trimethyltin or colchicine in rats, and in human Alzheimer's disease.

Several inhibitors of calpain have been described including peptide aldehydes such as Ac-Leu-Leu-Nle-H and leupeptin (Ac-Leu-Leu-Arg-H), as well as epoxysuccinates such as E-64. These compounds are not especially useful at inhibiting calpain in neural tissue *in vivo* because they are poorly membrane permeant and, accordingly, are not likely to cross the blood brain barrier very well. Also, many of these inhibitors have poor specificity and will inhibit a wide variety of proteases in addition to calpain. In addition, other classes of compounds which inhibit cysteine proteases include peptide diazomethyl ketone (Rich, D. H., in *Protease Inhibitors*, Barrett A. J., and Salversen, G., Eds., Elsevier, New York, 1986, pp 153-178; incorporated herein by reference). Peptide diazomethyl ketones are potentially carcinogenic and are thought to be poorly membrane permeant and to have low specificity. Thus, no effective therapy has yet been developed for most neurodegenerative diseases and conditions. Millions of individuals suffer from neurodegenerative diseases and thus, there is a need for therapies effective in treating and preventing these diseases and conditions.

Cathepsin B is involved in muscular dystrophy, myocardial tissue damage, tumor metastasis, and bone resorption. In addition, a number of viral processing enzymes, which are essential for viral infection, are cysteine proteases. Inhibitors of cysteine proteases would have multiple therapeutic uses.

Ketoesters. A few amino acid and peptide ketoesters and ketoacids have been previously reported. Cornforth and Cornforth [*J. Chem. Soc.*, 93-96 (1953); incorporated herein by reference] report the synthesis of the ketoacids $PhCH_2CO$-Gly-CO-OH and Ac-Gly-CO-OH upon hydrolysis of heterocyclic molecules. Charles et al. [*J. Chem. Soc. Perkin I*, 1139-1146 (1980); incorporated herein by reference] use ketoesters for the synthesis of bicyclic heterocycles. They report the synthesis of *n*-BuCO-Ala-CO-OEt, PrCO-Ala-CO-OEt, cyclopentylCO-Ala-CO-OEt, PrCO-PhGly-CO-OEt, and Bz-Ala-CO-OEt. Hori et al. [*Peptides: Structure and Function-Proceedings of the Ninth American Peptide Symposium* (Deber, Hruby, and Kopple, Eds.) Pierce Chemical Co., pp 819-822 (1985); incorporated herein by reference] report Bz-Ala-CO-OEt, Bz-Ala-CO-OH, Z-Ala-Ala-Abu-CO-OEt, Z-Ala-Ala-Abu-CO-OBzl, and Z-Ala-Ala-Ala-Ala-CO-OEt (Abu = 2-aminobutanoic acid or α-aminobutyric acid) and report that these compounds inhibit elastase. Trainer [*Trends Pharm. Sci.* 8, 303-307 (1987); incorporated herein by reference] comments on one of this compounds. Burkhart, J., Peet, N. P., and Bey, P. [*Tetrahedron Lett.* 29, 3433-3436 (1988); incorporated herein by reference] report the synthesis of Z-Val-Phe-CO-OMe and Bz-Phe-CO-OMe.

Mehdi et al. [*Biochem. Biophys. Res. Comm.* 166, 595-600 (1990); incorporated herein by reference] report the inhibition of human neutrophil elastase and cathepsin G by peptide α-ketoesters. Angelastro et al., [*J. Med. Chem.* 33. 13-16 (1990); incorporated herein by reference] report some α-ketoesters which are inhibitors of calpain and chymotrypsin. Hu and Abeles [*Arch. Biochem. Biophys.* 281, 271-274 (1990); incorporated herein by reference] report some peptidyl α-ketoamides and α-ketoacids which are inhibitors of cathepsin B and

papain. Peet et al. [*J. Med. Chem.* 33, 394-407 (1990); incorporated herein by reference] report some peptidyl α-ketoesters which are inhibitors of porcine pancreatic elastase, human neutrophil elastase, and rat & human neutrophil cathepsin G.

Ketoamides. A single peptide ketoamide is reported in the literature by Hu and Abeles [*Arch. Biochem. Biophys.* 281, 271-274 (1990)]. This compound Z-Phe-NHCH$_2$CO-CO-NH-Et or Z-Phe-Gly-CO-NH-Et is reported to be an inhibitor of papain (K_I = 1.5 μM) and cathepsin B (K_I = 4 μM).

SUMMARY OF THE INVENTION

We have discovered that peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives are a novel group of inhibitors for serine proteases and cysteine proteases. Inhibitors are compounds that reduce or eliminate the catalytic activity of the enzyme. We have discovered that peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives, which have an amino acid sequence similar to that of good substrates for a particular protease, are good inhibitors for that protease. Thus, we are able to predict the structure of new inhibitors for other serine and cysteine proteases based on knowledge of their substrate specificities.

We have discovered some peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives which are specific inhibitors for trypsin, elastase, chymotrypsin, granzymes, and other serine proteases, and some of the derivatives which are general inhibitors for groups of serine proteases. Trypsin and trypsin-like enzymes normally cleave peptide bonds in proteins and peptides where the amino acid residue on the carbonyl side of the split bond (P_1 residue) is Lys or Arg. Peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives which have Lys or Arg at P_1 are thus good inhibitors for these enzymes. Elastase and elastase-like enzymes cleave peptide bonds where the P_1 amino acid is Ala, Val, Ser, Leu and other similar amino acids. Inhibitors with these residues at P_1 are good elastase inhibitors. Chymotrypsin and chymotrypsin-like enzymes hydrolyze peptide bonds where P_1 amino acid is Trp, Tyr, Phe, Met, Leu or other amino acid residues which contain aromatic or large alkyl side chains. Inhibitors with these residues at P_1 are good chymotrypsin and chymase inhibitors. All of the above enzymes have extensive secondary specificity and recognize amino acid residues removed from the P_1 residue.

The new protease inhibitors, especially the elastase inhibitors, trypsin inhibitors, and chymase inhibitors are useful for controlling tissue damage and various inflammatory conditions mediated by proteases such as blistering. The inhibitors for blood coagulation enzymes are useful anticoagulants and could be used to treat thrombosis.

The peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives are also useful *in vitro* for inhibiting trypsin, elastase, chymotrypsin and other serine proteases of similar specificity, and for inhibiting serine proteases in general. The inhibitors can be used to identify new proteolytic enzymes encountered in research. They can also be used in research

and industrially to prevent undesired proteolysis that occurs during the production, isolation, purification, transport and storage of valuable peptides and proteins. Such proteolysis often destroys or alters the activity and/or function of the peptides and proteins. Uses would include the addition of the inhibitors to antibodies, enzymes, plasma proteins, tissue extracts or other proteins and peptides which are widely sold for use in clinical analyses, biomedical research, and for many other reasons. For some uses a specific inhibitor would be desirable, while in other cases, an inhibitor with general specificity would be preferred.

The peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives are also novel and potent inhibitors of cysteine proteases including calpains, cathepsin B, and papain. The calpain inhibitors are useful for treatment of various neurodegenerative diseases and conditions, including ischemia, stroke, and Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Peptide α-ketoesters, peptide α-ketoacids, and peptide α-ketoamides are transition state analog inhibitors for serine proteases and cysteine proteases. Peptide ketoesters containing hydrophobic amino acid residues in the P_1 site have been found to be excellent inhibitors of several serine proteases including human leukocyte elastase, porcine pancreatic elastase, human leukocyte cathepsin G, and bovine chymotrypsin. Peptide ketoesters containing amino acid residue with cationic side chain in the P_1 site have been found to be excellent inhibitors of several serine proteases including bovine trypsin, bovine thrombin, human plasma kallikrein, porcine pancreatic kallikrein, human factor XIa and human plasmin. Peptide ketoesters containing amino acid residues with hydrophobic side chain at the P_1 site have also been found to be excellent inhibitors of several cysteine proteases including papain, cathepsin B and calpain. These structures may be used *in vivo* to treat diseases such as emphysema, adult respiratory distress syndrome, rheumatoid arthritis and pancreatitis which result from uncontrolled proteolysis by elastase, chymotrypsin, trypsin and related serine proteases. These inhibitors may be used *in vitro* to prevent proteolysis which occurs in the process of production, isolation, purification, storage or transport of peptides and proteins. These inhibitors may be useful as therapeutic agents for treatment of neurodegeneration, viral infections, muscular dystrophy, myocardial tissue damage, tumor metastasis, and bone resorption.

The novel class of peptide α-ketoamides have the following structural formula:

$$M_1\text{-AA-NH-CHR}_2\text{-CO-CO-NR}_3\text{R}_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl,

phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 is selected from the group consisting of C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, and C_{1-8} branched and unbranched fluoroalkyl;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

The novel class of peptide α-ketoamides also have the following structural formula:

M_1-AA_2-AA_1-CO-NR_3R_4

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-

ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

The novel class of peptide α-ketoamides also have the following structural formula:

$$M_1\text{-AA-AA-AA-CO-NR}_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine,

tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

The novel class of peptide α-ketoamides also have the following structural formula:

$$M_1\text{-AA-AA-AA-AA-CO-NR}_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

The novel class of peptide α-ketoamides also have the following structural formula:

$$M_1\text{-AA-CO-NR}_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attacned 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

The novel class of peptide α-ketoacids have the following structural formula:

M_1-AA-NH-CHR_2-CO-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

The novel class of peptide α-ketoacids also have the following structural formula:

$$M_1\text{-}AA_2\text{-}AA_1\text{-}CO\text{-}OH$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-}

10 alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

The novel class of peptide α-ketoacids also have the following structural formula:

M_1-AA-AA-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

The novel class of peptide α-ketoacids also have the following structural formula:

M_1-AA-AA-AA-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y_1-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y_1 is selected from the group consisting of C_{2-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

The novel class of peptide α-ketoacids also have the following structural formula:

M_1-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y_2-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y_2 is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

The novel class of peptide α-ketoesters have the following structural formula:

$$M_1\text{-}AA_2\text{-}AA_1\text{-}CO\text{-}O\text{-}R_1$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_1 is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The novel class of peptide α-ketoesters also have the following structural formula:

M_1-AA-NH-CHR_2-CO-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine. leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The novel class of peptide α-ketoesters also have the following structural formula:

M_3-AA-AA-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{2-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The novel class of peptide α-ketoesters also have the following structural formula:

M_3-AA-AA-NH-CHR_2-CO-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{1-10} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The novel class of peptide α-ketoesters also have the following structural formula:

M_3-AA_4-AA-AA-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic

acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;;

AA_4 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of leucine, isoleucine, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The novel class of peptide α-ketoesters also have the following structural formula:

M_1-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y is selected from the group consisting of C_{6-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10}

alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

The following compounds are representatives of the invention:

Z-Leu-Phe-CONH-Et
Z-Leu-Phe-CONH-nPr
Z-Leu-Phe-CONH-nBu
Z-Leu-Phe-CONH-iBu
Z-Leu-Phe-CONH-Bzl
Z-Leu-Phe-CONH-$(CH_2)_2$Ph
Z-Leu-Abu-CONH-Et
Z-Leu-Abu-CONH-nPr
Z-Leu-Abu-CONH-nBu
Z-Leu-Abu-CONH-iBu
Z-Leu-Abu-CONH-Bzl
Z-Leu-Abu-CONH-$(CH_2)_2$Ph
Z-Leu-Abu-CONH-$(CH_2)_3$-N(CH_2CH_2)$_2$O
Z-Leu-Abu-CONH-$(CH_2)_7CH_3$
Z-Leu-Abu-CONH-$(CH_2)_2$OH

Z-Leu-Abu-CONH-$(CH_2)_2O(CH_2)_2OH$
Z-Leu-Abu-CONH-$(CH_2)_{17}CH_3$
Z-Leu-Abu-CONH-CH_2-$C_6H_3(OCH_3)_2$
Z-Leu-Abu-CONH-CH_2-C_4H_4N
Bz-DL-Ala-COOEt
Bz-DL-Ala-COOBzl
Bz-DL-Ala-COO-*n*-Bu
Bz-DL-Ala-COOH
Bz-DL-Phe-COOEt
Bz-DL-Ala-$COOCH_2$-C_6H_4-CF_3 (para)
Bz-DL-Arg-COOEt
Bz-DL-Lys-COOEt
Bz-DL-Lys-COOH
Z-Ala-DL-Ala-COOEt
Z-Ala-DL-Ala-COOBzl
Z-Ala-DL-Ala-COO-*n*-Bu
MeO-Suc-Ala-DL-Ala-COOMe
Z-Leu-Nva-COOEt
Z-Leu-Nle-COOEt
Z-Leu-Phe-COOEt
Z-Leu-Abu-COOEt
Z-Phe-DL-Phe-COOEt
H-Gly-DL-Lys-COOEt
H-Ala-DL-Lys-COOEt
H-Pro-DL-Lys-COOEt
H-Phe-DL-Lys-COOEt
Z-Ala-Ala-DL-Ala-COOEt
Z-Ala-Pro-DL-Ala-COOEt
Z-Ala-Ala-DL-Abu-COOEt
Z-Ala-Ala-DL-Abu-COOBzl
Z-Ala-Ala-DL-Abu-$COOCH_2$-C_6H_4-CF_3 (para)
MeO-Suc-Val-Pro-DL-Phe-COOMe
H-Leu-Ala-DL-Lys-COOEt
Z-Ala-Ala-Ala-DL-Ala-COOEt
MeO-Suc-Ala-Ala-Pro-DL-Abu-COOMe
Z-Leu-Phe-COOEt
2-Leu-Nva-COOEt
Z-Len-Abu-COOEt
PhCO-Abu-COOEt

$(CH_3)_2CH(CH_2)_2CO$-Abu-COOEt
$CH_3CH_2CH)_2CHCO$-Abu-COOEt
$Ph(CH_2)_6CO$-Abu-COOEt
Z-Leu-4-Cl-Phe-COOEt
Z-Leu-Leu-Abu-COOEt
Z-Leu-Leu-Phe-COOEt
2-NapSO_2-Leu-Abu-COOEt
2-NapSO_2-Leu-Leu-Abu-COOEt
Z-Leu-Met-CO_2Et
Z-Leu-NLeu-CO_2Et
Z-Leu-Phe-CO_2Bu
Z-Leu-Abu-CO_2Bu
Z-Leu-Phe-CO_2Bzl
Z-Leu-Abu-CO_2Bzl
Z-Leu-Phe-COOH
Z-Leu-Abu-COOH

Materials and Methods. HEPES, heparin, and A23187 were obtained from Calbiochem. Suc-Leu-Tyr-AMC and chromogenic substrates were obtained from Sigma. Calpain I was purified from human erythrocytes according to the method of Kitahara (Kitahara et al., *J. Biochem.* 95, 1759-1766) omitting the Blue-Sepharose step. Calpain II from rabbit muscle and cathepsin B were purchased from Sigma. Papain was purchased from Calbiochem.

Assay of Inhibitory Potency. Peptide α-ketoamides were assayed as reversible enzyme inhibitors. Various concentrations of inhibitors in Me_2SO were added to the assay mixture which contained buffer and substrate. The reaction was started by the addition of the enzyme and the hydrolysis rates were followed spectrophotometrically or fluorimetrically.

Calpain I from human erythrocytes and calpain II from rabbit were assayed using Suc-Leu-Tyr-AMC [Sasaki et al., *J. Biol. Chem.* 259, 12489-12494 (1984); incorporated herein by reference], and the AMC (7-amino-4-methylcoumarin) release was followed fluorimetrically (excitation at 380 nm, and emmision at 460 nm). Calpains were assayed in 25 mM Tris pH = 8.0, 10 mM $CaCl_2$. Fluorescence was followed using a Gilson FL-1A fluorometer or a Perkin-Elmer 203 Fluorescence spectrometer. Cathepsin B was assayed in 20 mM sodium acetate pH = 5.2, 0.5 mM dithiothreitol using Bz-Phe-Val-Arg-p-nitroanilide as substrate. Alternately, cathepsin B was assayed with Z-Arg-Arg-AFC [Barrett and Kirschke, *Methods Enzymol.* 80, 535-561 (1981); incorporated herein by reference], and the AFC (7-amino-4-trifluoromethylcoumarin) release was followed fluorimetrically (excitation at 400 nm and emmision at 505 nm). Papain was assayed in 100 mM KPO_4, 1 mM EDTA, 2.5 mM cysteine pH = 6.0 using Bz-Arg-AMC or Bz-Arg-NA [Kanaoka et al., *Chem. Pharm. Bull.* 25, 3126-3128 (1977); incorporated herein by reference] as a substrate. The AMC (7-amino-4-

methylcoumarin) release was followed fluorimetrically (excitation at 380 nm, and emmision at 460 nm). Enzymatic hydrolysis rates were measured at various substrate and inhibitor concentrations, and K_I values were determined by either Lineweaver-Burk plots or Dixon plots.

A 0.1 M Hepes, 0.5 M NaCl, pH 7.5 buffer was utilized for human leukocyte elastase (HLE), porcine pancreatic elastase (PPE), chymotrypsin and cathepsin G. A 0.1 Hepes, 0.01 M $CaCl_2$, pH 7.5 buffer was utilized for trypsin, plasmin, and coagulation enzymes. A 50 mM Tris·HCl, 2 mM EDTA, 5 mM cysteine, pH 7.5 was used as a buffer for papain. A 88 mM KH_2PO4, 12 mM Na_2HPO4, 1.33 mM EDTA, 2.7 mM cysteine, pH 6.0 solution was used as a buffer for cathepsin B. A 20 mM Hepes, 10 mM $CaCl_2$, 10 mM mercatoethanol, pH 7.2 buffer was utilized for calpain I and calpain II.

HLE and PPE were assayed with MeO-Suc-Ala-Ala-Pro-Val-NA and Suc-Ala-Ala-Ala-NA, respectively [Nakajima et al., J. Biol. Chem. 254, 4027-4032 (1979); incorporated herein by reference]. Human leukocyte cathepsin G and chymotrypsin A_α were assayed with Suc-Val-Pro-Phe-NA [Tanaka et al., Biochemistry 24, 2040-2047 (1985); incorporated herein by reference]. The hydrolysis of peptide 4-nitroanilides was measured at 410 nm [$\varepsilon_{410} = 8800$ $M^{-1}cm^{-1}$; Erlanger et al., Arch. Biochem. Biophys. 95, pp 271-278 (1961); incorporated herein by reference]. Trypsin, thrombin, human plasma kallikrein, porcine pancreatic kallikrein, human factor XIa, and human plasmin were assayed with Z-Arg-SBzl or Z-Gly-Arg-SBu-*i* [McRae et al., Biochemistry 20, 7196-7206 (1981); incorporated herein by reference]. All peptide thioester hydrolysis rates were measured with assay mixtures containing 4,4'-dithiodipyridine [$\varepsilon_{324} = 19800$ $M^{-1}cm^{-1}$; Grasetti & Murray, Arch. Biochem. Biophys. 119, pp 41-49 (1967); incorporated herein by reference]. Papain was assayed with Bz-Arg-AMC or Bz-Arg-NA [Kanaoka et al., Chem. Pharm. Bull. 25, 3126-3128 (1977); incorporated herein by reference]. The AMC (7-amino-4-methylcoumarin) release was followed fluorimetrically (excitation at 380 nm, and emmision at 460 nm). Cathepsin B was assayed with Z-Arg-Arg-AFC [Barrett and Kirschke, Methods Enzymol. 80, 535-561 (1981); incorporated herein by reference], and the AFC (7-amino-4-trifluoromethylcoumarin) release was followed fluorimetrically (excitation at 400 nm, and emmision at 505 nm). Calpain I from human erythrocytes and calpain II from rabbit were assayed using Suc-Leu-Tyr-AMC [Sasaki et al., J. Biol. Chem. 259, 12489-12494 (1984); incorporated herein by reference], and the AMC (7-amino-4-methylcoumarin) release was followed fluorimetrically (excitation at 380 nm, and emmision at 460 nm). Enzymatic hydrolysis rates were measured at various substrate and inhibitor concentrations, and K_I values were determined by either Lineweaver-Burk plots or Dixon plots.

Platelet membrane permeability assay. Calpain-mediated breakdown of spectrin was measured by quantitative densitometry of the calpain-specific 150/155 kDa spectrin fragment doublet [see Siman et al., *Proc. Natl. Acad. Sci. USA* 81, 3572-3576 (1984)]. Platelets were isolated by a modification of the method of Ferrell and Martin [*J. Biol. Chem.* 264, 20723-

20729 (1989)]. Blood (15-20 ml) was drawn from male Sprague-Dawley rats into 1/10th volume of 100 mM EDTA-citrate, and centrifuged 10 minutes at 2000 rpm in a clinical centrifuge at room temperature. The plasma was resuspended in 15 ml of buffer 1 (136 mM NaCl, 2.7 mM KCl, 0.42 mM NaH_2PO_4, 12 mM $NaHCO_3$, 2 mM $MgCl_2$, 2 mg/ml BSA (Sigma), 5.6 mM glucose, 22 mM Na_3citrate pH 6.5) and platelets were isolated at 2200 rpm at room temperature for 10 minutes. Platelets were washed once in 15 ml buffer 1, then resuspended to 10^7 cells/ml in buffer 2 (136 mM NaCl, 2.7 mM KCl, 0.42 mM NaH_2PO_4, 12 mM $NaHCO_3$, 2mM MgCl, 1 mg/ml BSA (Sigma), 5.6 mM glucose, 20 mM HEPES (Sigma) pH 7.4) and allowed to "rest" for a minimum of 10 minutes at room temperature before use.

Inhibitors were added from stock solutions made fresh in DMSO. 100 µl platelets, suspended to 10^7 cells/ml in buffer 2, were incubated with 1 µl of an inhibitor solution for 5 minutes at room temperature prior to the addition of 2 mM Ca^{2+} and 1 uM A23187. After 10 minutes total exposure to inhibitor (5 minutes exposure to ionophore) at room temperature, platelets were reisolated at 14,000 rpm for 10 sec in a Beckman microfuge, dissolved in SDS-PAGE sample buffer, and heated to 90 °C for 3 minutes.

Samples were subjected to SDS-PAGE in 4-12% gradient mini gels (Novex) and transferred to nitrocellulose (Schleicher and Schuell 0.45 um) by electroblotting. Filters were blocked for 10 minutes in 0.25% gelatin, 1% BSA, 0.25% triton X100, 0.9% NaCl, 10 mM Tris-Cl pH 7.5, incubated overnight in the same solution containing antibody to rat spectrin, washed 3 x 10 minutes with 10 mM Tris-Cl pH 7.5, 0.5% triton X 100, incubated 4 hours in wash buffer plus alkaline phosphatase conjugated goat anti-rabbit antibody (Biorad), and washed as above. Blots were developed using the Biorad AP conjugate substrate kit. Quantitative densitometry was used to obtain values for the intact spectrin bands and the 150/155 kDa breakdown product doublet.

Structure-Activity Relationships. Tables I and IV shows the inhibition constants (K_I) for human leukocyte elastase (HLE), porcine pancreatic elastase (PPE), chymotrypsin and cathepsin G. Tripeptide and tetrapeptide ketoesters with Ala, Abu, or Nva in the P_1 site are potent inhibitors of HLE and PPE. Amino acid and dipeptide ketoesters with Ala in the P_1 site are less potent than the tripeptides. Z-Ala-Ala-Abu-CO-OBzl is a potent inhibitor of elastases, and replacement of the Z group ($PhCH_2OCO$-) by $PhCH_2CH_2CO$-, $PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, and $PhCH_2NHCS$- would result in good inhibitor structures. Changing the R group of Z-Ala-Ala-Abu-CO-OR from ethyl to benzyl or *p*-trifluoromethylbenzyl results in equally potent inhibitors of HLE. However, replacement of ethyl by benzyl group in Z-Ala-Ala-CO-OEt makes a better elastase inhibitor. Amino acid and peptide ketoesters with Phe in the P_1 site are good inhibitors of chymotrypin and cathepsin G. MeO-Suc-Val-Pro-Phe-CO-OR is a potent inhibitor of chymotrypsin and cathepsin G, and replacement of methoxysuccinyl group by Z, benzoyl, $PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, or $PhCH_2NHCS$- would result in good inhibitors for chymotrypsin and cathepsin G.

Table II shows the inhibition constants (K_I) for trypsin, plasmin, and several blood coagulation enzymes. Amino acid and peptide ketoesters with Arg or Lys in the P_1 site are good inhibitors of trypsin, although they inhibit blood coagulation enzymes less potently. Bz-Arg-CO-OEt is a better thrombin inhibitor than Bz-Lys-CO-OEt, and tripeptides such as D-Phe-Pro-Arg-CO-OEt and Boc-D-Phe-Pro-Arg-CO-OEt are expected to be potent thrombin inhibitors because the interactions between the enzyme and inhibitor increase. H-Gly-Lys-CO-OEt inhibits thrombin better than Bz-Lys-CO-OEt, but this dipeptide ketoester is a less potent inhibitor for human plasma kallikrein. Therefore variation of the blocking group and amino acid sequence in the peptide ketoesters would result in the more specific inhibitors toward individual coagulation enzymes.

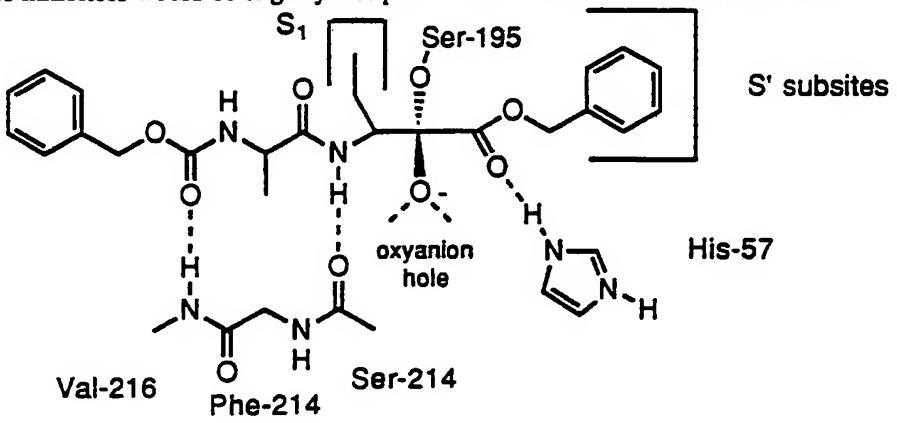
Tables III and IV shows the inhibition constants (K_I) for papain, cathepsin B, calpain I, and calpain II. Dipeptide ketoesters with Abu, Phe, or Nle in the P_1 site and Leu in the P_2 site are potent inhibitors of calpain I and calpain II. Z-Leu-Abu-CO-OEt is a better inhibitor of calpain than Z-Ala-Ala-Abu-CO-OEt by 500-1250 fold. Replacement of the Z group ($PhCH_2OCO$-) by similar groups such as $PhCH_2CH_2CO$-, $PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, and $PhCH_2NHCS$- would also result in good inhibitor structures. Extending the R group to include longer alkyl groups or alkyl groups substituted with phenyl groups would increase the membrane permeability of this inhibitor. Dipeptide and tripeptide ketoesters with small aliphatic amino acid residue or Phe in the P_1 site are also good inhibitors for papain and cathepsin B. Z-Phe-Phe-CO-OEt, Z-Ala-Ala-Nva-CO-OEt, and MeO-Suc-Val-Pro-Phe-CO-OMe are potent inhibitors of cathepsin B, and replacement of the Z ($PhCH_2OCO$-) or MeO-Suc- group by $PhCH_2CH_2CO$-, $PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, and $PhCH_2NHCS$- would also result in good inhibitor structures. Z-Ala-Ala-Abu-CO-OBzl inhibits papain ca. 30 fold less potently than Z-Ala-Ala-Abu-CO-OEt , thus changing the benzyl group to a smaller alkyl group such as methyl, or propyl would make better papain inhibitors.

Table IV shows the inhibition constants (K_I) for cathepsin B, calpain I, and calpain II with peptide ketoamides. Dipeptide α-ketoamides with Abu and Phe in the P_1 site and Leu in the P_2 site are potent inhibitors of calpain I and calpain II. Z-Leu-Abu-CONH-Et is a better inhibitor of calpain I than Z-Leu-Phe-CONH-Et by 14 fold. Replacement of the Z group ($PhCH_2OCO$-) by similar groups such as $PhCH_2CH_2CO$-, $PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, and $PhCH_2NHCS$- would also result in good inhibitor structures. The best inhibitor of calpain II is Z-Leu-Abu-CONH-$(CH_2)_2$-Ph. Changing the R_3 and R_4 groups significantly improves the inhibitory potency toward calpain II. The best dipeptide inhibitors are those which have long alkyl side chains (e.g. Z-Leu-Abu-CONH-$(CH_2)_7CH_3$), alkyl side chains with phenyl substituted on the alkyl group (e.g. Z-Leu-Abu-CONH-$(CH_2)_2$-Ph), or alkyl groups with a morpholine ring substituted on the alkyl group [e.g. Z-Leu-Abu-CONH-$(CH_2)_3$-Mpl, Mpl = $-N(CH_2CH_2)_2O$]. Dipeptide α-ketoamides with a small aliphatic amino acid residue or a Phe in the P_1 site are also good inhibitors for cathepsin B. The best inhibitor is Z-Leu-Abu-CONH-Et and replacement of the Z ($PhCH_2OCO$-) by $PhCH_2CH_2CO$-,

$PhCH_2CH_2SO_2$-, $PhCH_2NHCO$-, and $PhCH_2NHCS$- would also result in good inhibitor structures.

Peptide α-ketoamides and peptide ketoamides were substantially more stable in both plasma and liver than the corresponding peptide α-ketoesters (Table IV). The peptide α-ketoamides and ketoacids were also much more effective in the platelet assay. Extending the R_3 group to an alkyl group or an alkyl group substituted with a phenyl group increased the membrane permeability of the inhibitors as indicated by increased potency in the platelet assay.

Inhibition Mechanism. A crystal structure of one α-ketoester bound into the active site of porcine pancreatic elastase has been completed and a schematic drawing of the interactions observed is shown below. The active site Ser-195 oxygen of the enzyme has added to the carbonyl group of the ketoester to form a tetrahedral intermediate which is stabilized by interactions with the oxyanion hole. This structure resembles the tetrahedral intermediate involved in peptide bond hydrolysis and proves that α-ketoesters are transition-state analogs. His-57 is hydrogen bonded to the carbonyl group of the ester functional group, the peptide backbone on a section of PPE's backbone hydrogen bonds to the inhibitor to form a β-sheet, and the benzyl ester is directed toward the S' subsites. The side chain of the P_1 amino acid residue is located in the S_1 pocket of the enzyme. Interactions with ketoamides would be similar except for that there would be the possibility of forming an additional hydrogen bond with the NH group of the ketoamide functional group if R_3 or R_4 was H. If R_3 and/or R_4 are longer substituents, then they would make favorable interactions with the S' subsites of the enzyme. In the case of ketoacids, there would be no R group to interact with the S' subsites and these inhibitors would be slightly less potent than the ketoesters and ketoamides.



The active site of cysteine proteases share several features in common with serine proteases including an active site histidine residue. In place of the Ser-195, cysteine proteases have an active site cysteine residue which would add to the ketonic carbonyl group of the peptide keto acids, keto esters, or ketoamides to form an adduct very similar to the structure depicted above except with a cysteine residue replacing the serine-195 residue. Additional

interactions would occur between the extended substrate binding site of the cysteine protease and the inhibitor which would increase the binding affinity and specificity of the inhibitors.

Inhibitor Design and Selection. The peptide and amino acid α-ketoester, α-ketoacid, and α-ketoamide derivatives, as shown in the above crystal structure, bind to the enzymes using many of the interactions that are found in complexes of a particular individual enzyme with its substrates. In order to design an inhibitor for a particular serine or cysteine protease, it is necessary to: 1) find the amino acid sequences of good peptide substrates for that enzyme, and 2) place those or similar amino acid sequences into a α-ketoester, α-ketoacid, or α-ketoamide structure. Additional interactions with the enzyme can be obtained by tailoring the R group of the inhibitor to imitate the amino acid residues which are preferred by an individual protease at the S_1' and S_2' subsites. For example, ketoesters with R = branched alkyl groups would interact effectively with serine and cysteine proteases which prefer Leu, Ile, and Val residues at P_1' and/or P_2', while ketoesters and amides with R = alkyl substituted with phenyl would interact effectively with serine and cysteine proteases which prefer Phe, Tyr, Trp residues at P_1' and/or P_2'. Likewise, the M_1 group can be tailored to interact with the S subsites of the enzyme. This design strategy will also work when other classes of peptide inhibitors are used in place of the peptide substrate to gain information on the appropriate sequence to place in the ketoester, ketoacid, or ketoamide inhibitor. Thus, we are able to predict the structure of new inhibitors for other serine and cysteine proteases based on knowledge of their substrate specificities. Once a good inhibitor structure for a particular enzyme is found, it is then possible to change other characteristics such as solubility or hydrophobicity by adding substituents to the M_1 or R, R_3, and R_4 groups.

Elastase is an enzyme which hydrolyzes most effectively tetra- and tripeptides having P_1 residues with small alkyl side chains such as Ala and Val. MeO-Suc-Ala-Ala-Ala-Val-NA and Z-Ala-Ala-Ala-Ala-NA are good substrates (NA = 4-nitroanilide). Thus the corresponding α-ketoesters Z-Ala-Ala-Ala-DL-Ala-COOEt and MeO-Suc-Ala-Ala-Pro-DL-Abu-COOMe are excellent elastase inhibitors. Suc-Phe-Leu-Phe-NA is an excellent substrate for chymotrypsin, cathepsin G, and mast cell chymases. Thus, the corresponding α-ketoester is an excellent inhibitor for these chymotrypsin-like enzymes. In the case of the cysteine protease calpain, a good inhibitor sequence is Ac-Leu-Leu-Nle-H. We have found that ketoesters related in structure such as Z-Leu-Abu-CO-OEt and Z-Leu-Nle-CO-OEt are potent inhibitors for calpain. We have also found that ketoamides related in structure such as Z-Leu-Abu-CO-NR_3R_4 and Z-Leu-Phe-CO-NR_3R_4 are potent inhibitors for calpain.

The following structures are predicted to be potent inhibitors for the listed enzymes. The inhibitor sequences were obtained from peptide substrate and/or inhibitor sequences in the protease literature.

Z-Gly-Leu-Phe-CO-Q-R	for cathepsin G and RMCP II
MeO-Suc-Ala-Ala-Pro-Met-CO-Q-R	for cathepsin G
Boc-Ala-Ala-Asp-CO-Q-R	for human lymphocyte granzyme B

Suc-Pro-Leu-Phe-CO-Q-R and Boc-Ala-Ala-Phe-CO-Q-R	for RMCP I (RMCP = rat mast cell protease)
Boc-Gly-Leu-Phe-CO-Q-R, Suc-Phe-Leu-Phe-CO-Q-R	for human and dog skin chymase
Boc-Ala-Ala-Glu-CO-Q-R	for S. aureus V-8 protease
Z-Gly-Gly-Pro-CO-Q-R	for human prolyl endopeptidase
Ala-Pro-CO-Q-R	for DPP IV
Suc-Ala-Ala-Pro-Val-CO-Q-R	for PPE
Suc-Lys(Cbz)-Val-Pro-Val-CO-Q-R, adamantyl-SO_2-Lys($COCH_2CH_2CO_2H$)-Ala-Val-CO-Q-R, adamantyl-CH_2CH_2OCO-Glu(O-*t*-Bu)-Pro-Val-CO-Q-R, and adamantyl-SO_2-Lys(CO-$C_6H_4CO_2H$)-Ala-Val-CO-Q-R	for human leukocyte (neutrophil) elastase
Suc-Ala-Ala-Pro-Leu-CO-Q-R	for elastolytic proteinase from "Schistosoma mansoni"
Glu-Phe-Lys-CO-Q-R and Dns-Ala-Phe-Lys-CO-Q-R	for plasmin
D-Val-Gly-Arg-CO-Q-R and Dns-Glu-Gly-Arg-CO-Q-R	for factor Xa
Z-Phe-Arg-CO-Q-R and Z-Trp-Arg-CO-Q-R	for porcine pancreatic and human plasma kallikreins
Z-Lys-Arg-CO-Q-R	for human skin tryptase
Z-Gly-Arg-CO-Q-R	for human lung tryptase
Z-Ile-Ala-Gly-Arg-CO-Q-R	for factors IXa, Xa, XIa, XIIa and bovine plasma kallikrein
Glu-Gly-Arg-CO-Q-R	for urokinase
Dns-Phe-Pro-Arg-CO-Q-R	for plasminogen activator
Dns-Ile-Pro-Arg-CO-Q-R	for activated protein C
Z-Trp-Arg-CO-Q-R	for bovine factor IXa
Z-Gly-Arg-CO-Q-R	for bovine factor Xa and XIa
Z-Phe-Arg-CO-Q-R	for bovine factor XIIa
Dns-Glu-Gly-Arg-CO-Q-R	for human factor Xa
D-Phe-Pro-Arg-CO-Q-R, D-MePhe-Pro-Arg-CO-Q-R, and Boc-D-Phe-Pro-Arg-CO-Q-R	for human thrombin
Z-Phe-Gly-Arg-CO-Q-R	for trypsin
Cl-$C_6H_4CH_2OCO$-Phe-Gly-CO-O-*n*-Bu	for papain
$C_6H_5CH_2NHCO$-Gly-Phe-Gly-CO-O-*n*-Pr	for cathepsin B

where Q is O for ketoesters; and R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

where Q-R is OH for ketoacids.

where Q-R is $-NR_3R_4$ and R_3 & R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [$-N(CH_2CH_2)O$] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, $-CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, $-NH-CH_2CH_2$-(4-hydroxyphenyl), and $-NH-CH_2CH_2$-(3-indolyl).

In Vitro Uses. To use the above inhibitors *in vitro*, they are dissolved in an organic solvent such as dimethylsulfoxide or ethanol, and are added to an aqueous solution containing serine and/or cysteine proteases. The final concentration of the organic solvent should be less than 25%. The inhibitors may also be added as solids or in suspension. The serine and cysteine protease inhibitors of this invention would be useful in a variety of experimental procedures where proteolysis is a significant problem. Inclusion of these inhibitors in a radioimmunoassay experiments would result in higher sensitivity. The use of these inhibitors in plasma fractionation procedures would result in higher yields of valuable plasma proteins and would make purification of the proteins easier. The inhibitors disclosed here could be used in cloning experiments utilizing bacterial cultures, yeast and human cells to yield a purified cloned product in higher yield.

The novel compounds of this invention are effective in the prevention of unnecessary proteolysis caused by chymotrypsin-like, elastases, and trypsin-like enzymes in the process of purification, transport and storage of peptides and proteins as shown in Tables I, II, III, and IV by effective inhibition of chymotrypsin, elastase, trypsin, and other serine & cysteine proteases.

In Vivo Uses. Effective inhibitors of the proteolytic function of human leukocyte elastase and human cathepsin G (Tables I and IV) would have anti-inflammatory activity and can be used to treat and control emphysema, adult respiratory distress syndrome and rheumatoid arthritis. Effective inhibitors of the proteolytic function of chymotrypsin and pancreatic elastase (Tables I and IV) are effective for therapeutic use in treatment of pancreatitis.

Various α-ketoesters have anticoagulant activity as shown in Table II by effective inhibition of the proteolytic function of blood coagulation enzymes in Hepes buffer. Other

peptide α-ketoesters have anti-tumor activity as shown in Table II by the effective inhibition of the proteolytic function of human plasma plasmin.

Peptide α-ketoesters can be used to control protein turnover, muscular dystrophy, myocardial tissue damage, tumor metastasis, and bone resorption as shown in Tables III and IV by effective inhibition of lysosomal cathepsin B in buffer. Peptide α-ketoesters can also be used as neuroprotectants or for the treatment of ischemia, stroke or Alzheimer's disease as shown in Tables III and IV by effective inhibiton of calpain I and calpain II.

Considerable evidence has shown that leukocyte elastase and/or related enzymes play a role in tumor cell metastasis [Salo et al., *Int. J. Cancer* 30, pp 669-673 (1973); Kao et al., *Biochem. Biophys. Res. Comm.* 105, pp 383-389 (1982); Powers, J. C. in Modification of Proteins, R. E. Feeney and J. R. Whitaker, eds., Adv. Chem. Ser 198, Amer. Chem. Soc., Wash., D. C. pp 347-367 (1982); all incorporated herein by reference], therefore it is suggested that compounds of this invention may have anti-tumor activity.

Pulmonary emphysema is a disease characterized by progressive loss of lung elasticity due to the destruction of lung elastin and alveoli. The destructive changes of lung parentchyma associated with pulmonary emphysema are caused by uncontrolled proteolysis in lung tissues [Janoff, *Chest* 83, 54-58 (1983); incorporated herein by reference]. A number of proteases have been shown to induce emphysema in animals [Marco et al., *Am. Rev. Respir. Dis.* 104, 595-598 (1971); Kaplan, *J. Lab. Clin. Med.* 82, 349-356 (1973); incorporated herein by reference], particularly human leukocyte elastase [Janoff, ibid 115, 461-478 (1977); incorporated herein by reference]. Leukocyte elastase and other mediators of inflammation also appear to play a role in diseases such as mucocutaneous lymph node syndrome [Reiger et al., *Eur. J. Pediatr.* 140, 92-97 (1983); incorporated herein by reference] and adult respiratory distress syndrome [Stockley, *Clinical Science* 64, 119-126 (1983); Lee et al., *N. Eng. J. Med.* 304, 192-196 (1981); Rinaldo, ibid 301, 900-909 (1982); incorporated herein by reference].

It is known that *in vitro* activity of elastase inhibitors correlates with *in vivo* activity in animal models of emphysema and inflammation [Otterness et al., editors, Advances in Inflammation Research, Vol. 11, Raven Press 1986; incorporated herein by reference]. Prophylactic administration of an inhibitor of elastase significantly diminishes the extent of elastase-induced emphysema [Kleinerman et al., *Am. Rev. Resir. Dis.* 121, 381-387 (1980); Lucey et al., *Eur. Respir. J.* 2, 421-427 (1989); incorporated herein by reference]. Thus the novel inhibitors described here should be useful for the treatment of emphysema and inflammation. Elastase inhibitors have been used orally, by injection, or by instillation in the lungs in animal studies (Powers, *Am. Rev. Respir. Dis.*, 127, s54-s58 (1983); Powers and Bengali, *Am. Rev. Respir. Dis.* 134, 1097-1100 (1986); these two articles are incorporated herein by reference). The inhibitors described above can be used by any of these routes.

Drug Delivery. For therapeutic use, the peptide α-ketoesters, α-ketoamides, and α-ketoacids may be administered orally, topically or parenterally. The term parenteral as used includes subcutaneous injection, intravenous, intramuscular, intrasternal injection or infusion

techniques. The dosage depends primarily on the specific formulation and on the object of the therapy or prophylaxis. The amount of the individual doses as well as the administration is best determined by individually assessing the particular case.

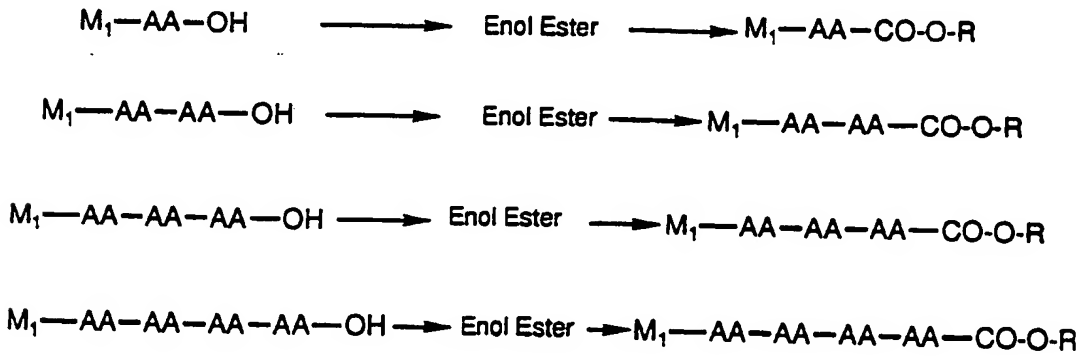
The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules or syrups or elixirs. Dosage levels of the order to 0.2 mg to 140 mg per kilogram of body weight per day are useful in the treatment of above-indicated conditions (10 mg to 7 gms per patient per day). The amount of active ingredient that may be combined with carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

For injection, the therapeutic amount of the peptide α-ketoesters, α-ketoamides, and α-ketoacids or their pharmaceutically acceptable salts will normally be in the dosage range from 0.2 to 140 mg/kg of body weight. Administration is made by intravenous, intramuscular or subscutaneous injection. Accordingly, pharmaceutical compositions for parenteral administration will contain in a single dosage form about 10 mg to 7 gms of the compounds per dose. In addition to the active ingredient, these pharmaceutical compositions will usually contain a buffer, e.g. a phosphate buffer which keeps the pH in the range from 3.5 to 7 and also sodium chloride, mannitol or sorbitol for adjusting the isotonic pressure.

A composition for topical application can be formulated as an aqueous solution, lotion, jelly or an oily solution or suspention. A composition in the form of an aqueous solution is obtained by dissolving the compounds of this invention in aqueous buffer solution of pH 4 to 6.5 and if desired, adding a polymeric binder. An oily formulation for topical application is obtained by suspending the compounds of this invention in an oil, optionally with the addition of a swelling agent such as aluminium stearate and/or a surfactant.

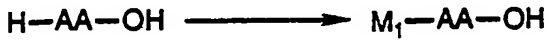
SYNTHETIC METHODS

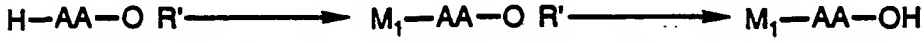
The ketoester inhibitors are prepared by a two step Dakin-West procedure. This procedure can be utilized with either amino acid derivatives, dipeptide derivatives, tripeptide derivatives, or tetrapeptide derivatives as shown in the following scheme.



The precursor peptide can be prepared using standard peptide chemistry which is well described in publications such as *The Peptides. Analysis, Synthesis, Biology,* Vol. 1-9, published in 1979-1987 by Academic Press and Houben-Weyl Methoden der Organischen Chemie, Vol. 15, Parts 1 and 2, *Synthese von Peptiden,* published by Georg Thieme Verlag, Stuttgart in 1974 (both references incorporated herein by reference).

The M_1 group can be introduced using a number of different reaction schemes. First it could be introduced directly on an amino acid as shown in the following scheme (top), or the M_1 group could be introduced by reaction with an amino acid ester, followed by removal of the ester group to give the same product (bottom).





The techniques for introduction of the M_1 group is well documented in the The Peptides, Houben-Weyel, and many other textbooks on organic synthesis. For example reaction with cyanate or *p*-nitrophenyl cyanate would introduce a carbamyl group (M_1 = NH_2CO-). Reaction with Me_2NCOCl would introduce the Me_2NCO- group. Reaction with *p*-nitrophenyl thiocarbamate would introduce a thio carbamyl group ($M_1 = NH_2CS$-). Reaction with NH_2SO_2Cl would introduce the NH_2SO_2- group. Reaction with Me_2NSO_2Cl would introduce the Me_2NSO_2- group. Reaction with a substituted alkyl or aryl isocyanate would introduce the X-NH-CO- group where X is a substituted alkyl or aryl group. Reaction with a substituted alkyl or aryl isothiocyanate would introduce the X-NH-CS- group where X is a substututed alkyl or aryl group. Reaction with X-SO_2-Cl would introduce the X-SO_2- group. Reaction with a substituted alkyl or aryl acid chloride would introduce an acyl group (M = X-CO-). For example, reaction with MeO-CO-CH_2CH_2-CO-Cl would give the X-CO- group where X is a C_2 alkyl substituted with a C_1 alkyl-OCO- group. Reaction with a substituted alkyl or aryl thioacid chloride would introduce a thioacyl group (M = X-CS-). Reaction with an a substituted alkyl or aryl sulfonyl chloride would introduce an X-SO_2- group. For example reaction with dansyl chloride would give the X-SO_2- derivative where X was a naphthyl group mono substituted with a dimethylamino group. Reaction with a substituted alkyl or aryl chloroformate would introduce a X-O-CO- group. Reaction with a substituted alkyl or aryl chlorothioformate would introduce a X-O-CS-. There are many alternate reaction schemes which could be used to introduce all of the above M_1 groups to give either M_1-AA-OH or M_1-AA-OR'.

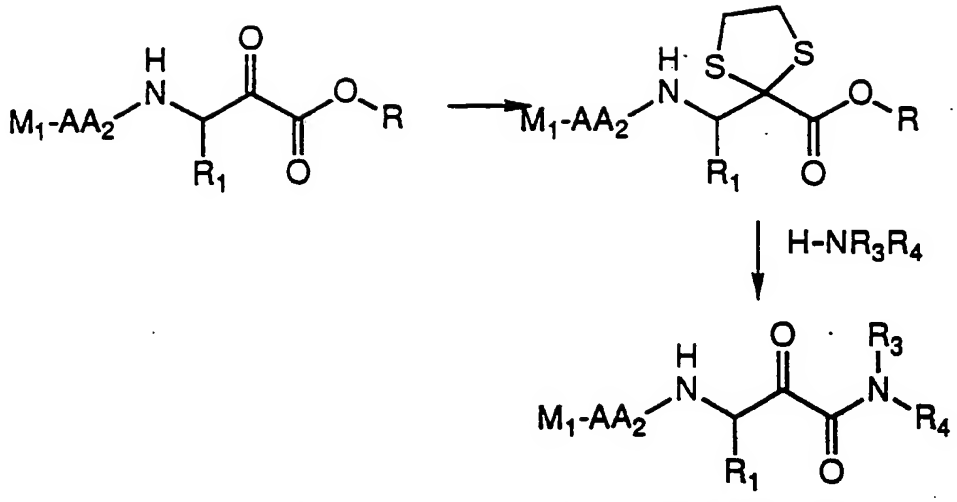
The M_1-AA-OH derivatives could then be used directly in the Dakin-West reaction or could be converted into the dipeptides, tripeptides, and tetrapeptides M_1-AA-AA-OH, M_1-AA-AA-AA-OH, or M_1-AA-AA-AA-AA-OH which could be be used in the Dakin-West reaction. The substituted peptides M_1-AA-AA-OH, M_1-AA-AA-AA-OH, or M-AA-AA-AA-AA-OH could also be prepared directly from H-AA-AA-OH, H-AA-AA-AA-OH, or H-AA-AA-AA-

AA-OH using the reactions described above for introduction of the M group. Alternately, the M group could be introduced by reaction with carboxyl blocked peptides to give M_1-AA-AA-OR', M_1-AA-AA-AA-OR', or M_1-AA-AA-AA-AA-OR', followed by the removal of the blocking group R'.

The R_1 group in the ketoester structures is introduced during the Dakin-West reaction by reaction with an oxalyl chloride Cl-CO-CO-O-R. For example, reaction of M_1-AA-AA-OH with ethyl oxalyl chloride Cl-CO-CO-O-Et gives the keto ester M_1-AA-AA-CO-O-Et. Reaction of M_1-AA-AA-AA-AA-OH with Cl-CO-CO-O-Bzl would give the ketoester M_1-AA-AA-AA-AA-CO-O-Bzl. Clearly a wide variety of R groups can be introduced into the ketoester structure by reaction with various alkyl or arylalkyl oxalyl chlorides (Cl-CO-CO-O-R). The oxalyl chlorides are easily prepared by reaction of an alkyl or arylalkyl alcohol with oxalyl chloride Cl-CO-CO-Cl. For example, Bzl-O-CO-CO-Cl and *n*-Bu-O-CO-CO-Cl are prepared by reaction of respectively benzyl alcohol and butanol with oxalyl chloride in yields of 50% and 80% [Warren, C. B., and Malee, E. J., J. Chromatography 64, 219-222 (1972); incorporated herein by reference].

Ketoacids M_1-AA-CO-OH, M_1-AA-AA-CO-OH, M_1-AA-AA-AA-CO-OH, M_1-AA-AA-AA-AA-CO-OH, are generally prepared from the corresponding ketoesters M_1-AA-CO-OR, M_1-AA-AA-CO-OR, M_1-AA-AA-AA-CO-OR, M_1-AA-AA-AA-AA-CO-OR by alkaline hydrolysis. In some cases, it may be necessary to use other methods such as hydrogenolysis of a benzyl group (R = Bzl) or acid cleavage (R = *t*-butyl) to obtain the ketoacid. The alternate methods would be used when the M group was labile to alkaline hydrolysis.

Ketoamides M_1-AA-CO-NR_3R_4, M-AA-AA-CO-NR_3R_4, M-AA-AA-AA-CO-NR_3R_4, M-AA-AA-AA-AA-CO-NR_3R_4 were prepared indirectly from the ketoesters. The ketone carbonyl group was first protected as shown in the following scheme and then the ketoamide was prepared by reaction with an amine H-NR_3R_4. The illustrated procedure should also work with other protecting groups. In addition, the corresponding ketoacid could be used as a precursor. Blocking the ketone carbonyl group of the ketoacid and then coupling with an amine H-NR_3R_4 using standard peptide coupling reagents would yield an intermediate which could then be deblocked to form the ketoamide.



General Synthetic Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken with a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were determined on a Varian Gemini 300. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Flash column chromatography was performed with Universal Scientific Inc. silica gel 0-63. Electron-impact mass spectra (MS) of novel compounds were determined with a Varian MAT 112S spectrometer. The purity of all compounds was checked by thin-layer chromatography on Baker Si250F silica gel plates using the following solvent system: A, $CHCl_3$:MeOH = 20:1 v/v; B, $CHCl_3$:MeOH = 100:1 v/v; C, AcOEt; D, $CHCl_3$:MeOH = 10:1 v/v; E, n-BuOH:AcOH:py:H_2O = 4:1:1:2 v/v; F, $CHCl_3$:MeOH = 5:1 v/v; G, AcOEt:MeOH = 10:1 v/v; H, $(i\text{-}Pr)_2O$; I, $CHCl_3$:MeOH:AcOH = 80:10:5 v/v; J, $CHCl_3$:MeOH:AcOH = 95:5:3 v/v; K, AcOEt:AcOH = 200:1 v/v; L, $CHCl_3$; M, $CHCl_3$:MeOH = 50:1 v/v

Amino acid methyl ester hydrochlorides were prepared according to M. Brenner et al.[*Helv. Chem. Acta* 33, 568 (1950); 36, 1109 (1953)] in a scale over 10 mmol or according to Rachele [*J. Org. Chem.* 28, 2898 (1963)] in a scale of 0.1-1.0 mmol.

	Yield (%)	mp (°C)	m.p. (literature)
DL-Nva-OCH_3·HCl,	100	113-116	116-117
L-Ile-OCH_3·HCl,	98	90-91	98-100
L-Phe-OCH_3·HCl,	98	159-161	158-160
DL-Abu-OCH_3·HCl,	100	148-150	150-151
L-Leu-OCH_3·HCl	100	145.5-146.5	147
DL-Nle-OCH_3·HCl	93	120-121	122-123
4-Cl-Phe-OCH_3·HCl	98	184-185 (decomp.)	185-186

N-Acylamino acids was synthesized via Schotten-Baumann reaction [M. Bergmann, L. Zervas, *Chem. Ber.* 65, 1192 (1932)] in the case when the acyl group was phenylsulphonyl, 2-naphthylsulphonyl or benzoyl.

	Yield (%)	mp (°C)	TLC (R_f, eluent)
2-NapSO_2-L-Leu-OH	49	115-116	0.58 I
2-NapSO_2-DL-Abu-OH	51	150-151	0.50 I
2-NapSO_2-L-Phe-OH	57	148-148.5	0.48 K
PheSO_2-DL-Abu-OH	44	142-143	0.51 K
PhCO-DL-Abu-OH	64	141-142	0.64 K

N-Acylamino acids with 4-methylpentanoic, 2-(1-propyl)pentanoic and 7-phenylheptanoic group was synthesized in a two step synthesis. The N-acylamino acid methyl ester was obtained first and then was hydrolysed to the free N-acylamino acid.

N-Acylamino Acid Methyl Esters (General Procedure). To a chilled (10 °C) slurry of the appropriate amino acid methyl ester hydrochloride (20 mmol) in 100 ml benzene was added slowly (temp. 10-15 °C) 40 mmol triethylamine or N-methylmorpholine and then the reaction mixture was stirred for 30 minutes at this temperature. Then 18 mmol of appropriate acid chloride (temp. 10-15 °C) was added slowly to the reaction mixture and the reaction mixture was stirred overnight at room temperature. The precipitated hydrochloride was filtered, washed on a funnel with 2 x 20 ml benzene, and the collected filtrate was washed successively with 2 x 50 ml 1 M HCl, 2 x 50 ml 5% $NaHCO_3$, 1 x 100 ml H_2O, 2 x 50 ml satd. NaCl and dried over $MgSO_4$. After evaporation of the solvent in vacuo (rotavaporator), the residue was checked for purity (TLC) and used for the next step (hydrolysis).

	Yield (%)	mp (°C)
$(CH_3)_2CH(CH_2)_2CO$-DL-Abu-OCH_3	80	oil
$(CH_3CH_2CH_2)_2CHCO$-DL-Abu-OCH_3	96	117-118
$Ph(CH_2)_6CO$-DL-Abu-OCH_3	72	oil

Hydrolysis (General Procedure). To a solution of 10 mmole of the appropriate N-acylamino acid methyl ester in 100 ml of methanol was added in one portion 11.25 ml of 1 M NaOH (11.25 mmol) and the reaction mixture was stirred three hours at room temperature. Then the reaction mixture was cooled to 0 °C (ice-salt bath) and acidified to pH = 2 with 1 M HCl aq. To this reaction mixture was added 100 ml ethyl acetate, transferred to a separatory funnel and organic layer separated. The water layer was saturated with solid NaCl or $(NH_4)_2SO_4$ and reextracted with 2 x 50 ml AcOEt. The collected organic layer was washed with 2 x 50 ml H_2O, decolorized with carbon, and dried over $MgSO_4$. After evaporation of the solvent in vacuo (rotavaporator), the residue was checked for purity (TLC) and in the case of contamination was crystallized from an appropriate solvent.

	Yield (%)	mp (°C)
$(CH_3)_2CH(CH_2)_2CO$-DL-Abu-OH	92	110.5-112
$(CH_3CH_2CH_2)_2$ CHCO-DL-Abu-OH	99	126-127 (n-octane)
$Ph(CH_2)_6CO$-DL-Abu-OH	89	110-112(n-octane)

N-Acyldipeptide methyl esters were synthesized via the HOBt-DCC method in a DMF solution [König and Geiger. *Chem. Ber.* 103, 788 (1970)].

	Yield (%)	mp (°C)	TLC (R_f, eluent)
Z-Leu-DL-NVa-OCH_3	80	112-113	0.37 B
Z-Leu-L-Phe-OCH_3	83	86-87	0.85 A
			0.39 B
Z-Leu-L-Ile-OCH_3	97	oil	0.79 A
			0.43 B
Z-Leu-DL-Abu-OCH_3	99	86-88	0.33 B
			0.26 H
Z-Leu-L-Leu-OCH_3	80	91-92	0.79 G
Z-Leu-DL-NLeu-OCH_3	97	111-111.5	
Z-Leu-4-Cl-Phe-OCH_3	65	112-132	0.77 J
		(liquid crystal?)	0.68 K
2-NapSO_2-Leu-DL-Abu-OCH_3	99	oil	0.59 A
2-NapSO_2-Leu-L-Leu-OCH_3	90	97-98.5	0.63 A

N-Acyldipeptides were obtained by hydrolysis of the appropriate methyl esters via a general hydrolysis procedure. In the case of N-sulphonyldipeptide methyl esters, 1 equivalent of the methyl ester was hydrolyzed with 2.25 equivalent of 1 molar NaOH because of form a sulfonamide sodium salt.

	Yield (%)	mp (°C)	TLC (R_f, eluent)
Z-Leu-DL-NVa-OH	100	117-118.5	0.11 A
Z-Leu-L-Phe-OH	92	105-106.5	0.28 C
			0.55 G
Z-Leu-L-ILe-OH	79	77-79	0.22 A
			0.52 C
Z-Leu-DL-Abu-OH	99	glass	0.61 G
Z-Leu-L-Leu-OH	97	glass	0.56 I
Z-Leu-DL-NLeu-OH	98	95-96	
Z-Leu-4-Cl-Phe-OH	87	104-114	0.48 K
		(liquid crystal?)	
2-NapSO_2-Leu-DL-Abu-OH	97.4	180-195 (decomp)	0.58 I
2-NapSO_2-Leu-L-Leu-OH	94.0	68-70	0.52 I

N-Acytripeptide methyl esters were synthesized via HOBt-DCC method in DMF solution [König and Geiger, *Chem. Ber.* 103, 788 (1970)].

	Yield (%)	mp (°C)	TLC (R_f, eluent)
Z-Leu-Leu-Abu-OCH_3	87	140-141.5	0.50 A
Z-Leu-Leu-Phe-OCH_3	76	158-159	0.83 J
2-NapSO_2-Leu-Leu-Abu-OCH_3	97	>200	0.52 A

N-Acyltripeptide were obtained through hydrolysis of the appropriate methyl esters via general hydrolysis procedure. In the case of N-sulphonyltripeptide methyl ester, 1 equivalent

of methyl ester was hydrolyzed with 2.25 equivalent of 1 molar NaOH to form the sulfonamide sodium salt.

	Yield	mp (°C)	TLC (Rf, eluent)	
Z-Leu-Leu-Abu-OH	97	glass	0.69	I
Z-Leu-Leu-Phe-OH	98	glass	0.44	K
2-NapSO_2-Leu-Leu-Abu-OH	85	193-195 (decomp)	0.53	I
			0.32	J

The following detailed examples are given to illustrate the invention and are not intended to limit it in any manner.

EXAMPLE 1

Z-Ala-DL-Ala-COOEt. This compound was synthesized by a modified Dakin-West procedure [Charles et al., *J. Chem. Soc. Perkin I*, 1139-1146, (1980)]. To a stirred solution of Z-Ala-Ala-OH (880 mg, 3 mmole), 4-dimethylaminopyridine (15 mg, 0.31 mmole), and pyridine (0.8 mL, 10 mmole) in tetrahydrofuran (3 mL) was added ethyl oxalyl chloride (0.7 mL, 6 mmole) at a rate sufficient to initiate refluxing. The mixture was gently refluxed for 3.5 h. The mixture was treated with water (3 mL) and stirred vigorously at room temperature for 30 min. The mixture was extracted with ethyl acetate. The organic extracts were dried and evaporated to obtain the residue (1.45 g). The residue was chromatographed on silica gel and eluted with CH_2Cl_2 to give the enol ester product, oil (500 mg, 37%); single spot on tlc, R_f^2 = 0.67 ($CHCl_3$:MeOH = 9:1); MS, m/e = 451 (M^++1). To a stirred suspension of the enol ester (210 mg, 0.47 mmol) in anhydrous ethanol (1 mL) at room temperature was added dropwise a solution of sodium ethoxide in ethanol until a clear yellow solution resulted. The ethanol was then removed and the residue was treated with ether. The ether solution was washed with water, dried, and evaporated to give a residue. This residue was chromatographed on a silica gel and the product was eluted with methylene chloride. The solvent was removed, and the peptide ketoester Z-Ala-DL-Ala-CO_2Et was obtained as an semi-solid (150 mg, 92 %); single spot on tlc, Rf1 0.58 ($CHCl_3$:MeOH = 5:1); MS, m/e = 351 (M^++1). Anal. Calcd. for $C_{17}H_{22}O_6N_2 \cdot 1/3\ H_2O$: C, 57.29; H, 6.22; N, 7.86. Found: C, 57.23; H, 6.36; N, 8.17.

EXAMPLE 2

Z-Ala-Ala-DL-Ala-CO_2Et. This compound was prepared from Z-Ala-Ala-Ala-OH using the same procedure as described in Example 1. The product was crystallized from ethyl ether in 23% yield; single spot on tlc, R_f^2 = 0.31 ($CHCl_3$:MeOH = 9:1); mp 143-144 °C; MS, m/e = 421 (M^+). Anal. Calcd. for $C_{20}H_{27}O_7N_3$: C, 56.99; H, 6.46; N, 9.97. Found: C, 56.96; H, 6.49; N, 9.92.

EXAMPLE 3

Z-Ala-Ala-DL-Abu-CO_2Et. This compound was prepared from Z-Ala-Ala-DL-Abu-OH in 11% yield by the procedure described in Example 1; single spot on tlc, R_f^2 = 0.60

($CHCl_3$:MeOH = 9:1); mp 111-113 °C; MS, m/e = 436 (M^++1). Anal. Calcd. for $C_{21}H_{29}O_7N_3 \cdot 1/3\ H_2O$: C, 57.13; H, 6.75; N, 9.51. Found: C, 57.38; H, 6.82; N, 9.62.

EXAMPLE 4

Z-Ala-Ala-DL-Nva-CO_2Et. This compound was prepared from Z-Ala-Nva-OH in 20% yield by the procedure described in Example 1; single spot on tlc, R_f^1 = 0.64 ($CHCl_3$:MeOH = 5:1); MS, m/e = 450 (M^++1). Anal. Calcd. for $C_{22}H_{31}O_7N_3 \cdot H_2O$: C, 56.51; H, 7.11; N, 8.99. Found: C, 56.42; H, 7.08; N, 9.06.

EXAMPLE 5

Z-Ala-Pro-DL-Ala-CO_2Et. This compound was prepared from Z-Ala-Pro-Ala-OH.dicyclohexylamine in 19% yield by the procedure described in Example 1; single spot on tlc, R_f^2 = 0.55 ($CHCl_3$:MeOH = 9:1); MS, m/e = 447 (M^+). Anal. Calcd. for $C_{22}H_{29}O_7N_3 \cdot 1/2$ H2O: C, 57.88; H, 6.62; N, 9.21. Found: C, 57.65; H, 6.68; N, 9.17.

EXAMPLE 6

Z-Ala-Ala-Ala-DL-Ala-CO_2Et. The compound was prepared from Z-Ala-Ala-Ala-Ala-OH in 7% yield by the procedure described in Example 1; single spot on tlc, R_f^2 =0.40 ($CHCl_3$:MeOH = 9:1); mp. 163-165 °C; MS, m/e = 493 (M^++1). Anal. Calcd. for $C_{23}H_{32}O_8N_4 \cdot 1/2\ H_2O$: C, 55.08; H, 6.63; N, 11.17. Found: C, 54.85; H, 6.53; N, 11.14.

EXAMPLE 7

Bz-DL-Phe-CO_2Et. This compound was prepared from Bz-Phe-OH in 36% yield by the procedure described in Example 1, oil, single spot on tlc, R_f^2 = 0.61 (CHCl3:MeOH = 9:1); MS, m/e = 325 (M^+). Anal. Calcd. for $C_{19}H_{19}O_4N.1/3\ H_2O$: C, 68.86; H, 5.98; N, 4.22. Found: C, 69.10; H, 6.09; N, 4.38.

EXAMPLE 8

MeO-Suc-Ala-DL-Ala-CO_2Me. This compound was prepared from MeO-Suc-Ala-Ala-OH in 22% yield by the same procedure as described in Example 1, except that sodium methoxide in methanol was used for enol ester hydrolysis, single spot on tlc, R_f^2 = 0.43 ($CHCl_3$:MeOH = 9:1); MS, m/e = 317 (M^++1). Anal. Calcd. for $C_{13}H_{20}O_7N_4.1/3\ H_2O$: C, 48.44; H, 6.46; N, 8.69. Found: C, 48.56; H, 6.39; N, 8.69.

EXAMPLE 9

MeO-Suc-Ala-Ala-Pro-DL-Abu-CO_2Me. This compound was prepared from MeO-Suc-Ala-Ala-Pro-DL-Abu-OH in 22% yield by the procedure described in Example 8; foam, single spot on tlc, R_f^1 = 0.66 ($CHCl_3$:MeOH = 5:1). Anal. Calcd. for $C_{22}H_{34}O_9N_4 \cdot H_2O$: C, 51.53; H, 7.02; N, 10.85. Found: C. 51.11; H, 7.03; N, 10.88.

EXAMPLE 10

MeO-Suc-Val-Pro-DL-Phe-CO_2Me. This compound was prepared from MeO-Suc-Val-Pro-Phe-OH in 42% yield by the same procedure as described in Example 8: foam, single spot on tlc, R_f^2 0.57 ($CHCl_3$:MeOH = 9:1); MS, m/e = 517 (M^+). Anal. Calcd. for $C_{26}H_{35}O_8N_3 \cdot 2/3$ H2O: C, 58.96; H, 6.90; N, 7.93. Found: C, 58.92; H, 6.96; N, 7.89.

EXAMPLE 11

Bz-DL-Ala-CO_2-*n*-Bu. This compound was prepared from Bz-Ala-OH in 45% yield by the procedure described in Example 1, except that n-butyl oxalylchloride was used for the Dakin-West reaction and sodium n-butoxide in n-butanol was used for enol ester hydrolysis; colorless oil, single spot on tlc, R_f^2 = 0.72 ($CHCl_3$:MeOH = 9:1); MS, m/e = 277 (M^+).

EXAMPLE 12

Bz-DL-Ala-CO_2Bzl. This compound was prepared from Bz-Ala-OH in 26% yield by the procedure described in Example 1, except that benzyl oxalyl chloride was used in place of ethyl oxayl chloride and sodium benzyloxide in benzyl alcohol was used for enol ester hydrolysis; single spot on tlc, R_f^2 =0.69 ($CHCl_3$:MeOH = 9:1); mp 95-97 °C; MS, m/e = 312 (M^++1). Anal. Calcd. for $C_{18}H_{17}O_4N \cdot 1/2\ H_2O$: C, 67.48; H, 5.66; N, 4.37. Found: C, 67.78; H, 5.55; N, 4.66.

EXAMPLE 13

Z-Ala-DL-Ala-CO_2-*n*-Bu. This compound was prepared from Z-Ala-Ala-OH in 14% yield by the procedure described in Example 1, except that n-butyl oxalyl chloride was used in the Dakin-West reaction and sodium n-butoxide was used for enol ester hydrolysis; oil, single spot on tlc, R_f^2 = 0.45 ($CHCl_3$:MeOH = 9:1); MS, m/e = 378 (M^+). Anal. Calcd. for $C_{19}H_{26}O_6N_2 \cdot 1/3\ H_2O$: C, 59.35; H, 7.00; N, 7.29. Found: C, 59.41; H, 7.03; N, 7.10.

EXAMPLE 14

Z-Ala-DL-Ala-CO_2Bzl. This compound was prepared from Z-Ala-Ala-OH in 36% yield by the procedure described in Example 1, except that benzyl oxalyl chloride was used in the Dakin-West reaction and sodium benzyloxide in benzyl alcohol was used for enol ester hydrolysis; single spot on tlc, R_f^2 = 0.55 ($CHCl_3$:MeOH = 9:1); MS, m/e = 413 (M^++1). Anal. Calcd. for $C_{22}H_{24}O_6N_2$: C, 64.06; H, 5.87; N, 6.79. Found: C, 63.79; H, 5.95; N, 6.72.

EXAMPLE 15

Z-Ala-Ala-DL-Abu-CO_2Bzl. This compound was prepared from Z-Ala-Ala-Abu-OH in 31% yield by the procedure described in Example 1, except that benzyl oxalyl chloride was used in the Dakin-West reaction and sodium benzyloxide in benzyl alcohol was used for enol ester hydrolysis; single spot on tlc, R_f^2 = 0.40 (CHCl3:MeOH = 9:1); mp 124-125 °C; MS, m/e = 498 (M^++1). Anal. Calcd. for $C_{26}H_{31}O_7N_3 \cdot 2/3\ H_2O$: C, 61.28; H, 6.39; N, 8.24. Found: C, 61.14; H, 6.65; N, 7.94.

EXAMPLE 16

Bz-DL-Ala-COOH. The hydrolysis procedure of Tsushima et al. [*J. Org. Chem.* 49, 1163-1169 (1984)] was used. Bz-DL-Ala-CO_2Et (540 mg, 2.2 mmol) was added to a solution of 650 mg of sodium bicarbonate in an aqueous 50% 2-propanol solution (7.5 mL of H_2O and 2-propanol) and stirred at 40 °C under nitrogen. After adding ethyl acetate and a saline solution to the reaction mixture, the aqueous layer was separated and acidified with 2N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and

the solvent was removed under reduced pressure. The crude hydrolysis product was chromatographed on silica gel and eluted with methylene chloride and methanol to obtain an oil (150 mg, 31%); single spot on tlc, R_f^4 = 0.68 (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2). Anal. Calcd. for $C_{11}H_{11}O_4N \cdot 3/4\ H_2O$: C, 56.28; H, 5.37; N, 5.97. Found: C, 56.21; H, 5.46; 5.66.

EXAMPLE 17

Z-Leu-DL-Nva-COOEt. This compound was prepared from Z-Leu-Nva-OH in 60 % yield by the procedure described in Example 1; oil, one spot on tlc, R_f = 0.49 ($CHCl_3$:MeOH = 20:1). NMR ($CDCl_3$) d: 0.91 (t, 9H), CH_3; 1.25 (t, 3H), CH_3; 1.38 (q, 2H), OCH_2CH_3; 1.64 (m, 6H), CH_2; 1.85 (m, 1H), $CH(CH_3)_2$; 4.34 (m, 1H) $CH_2CH(NHCOOCH_2Ph)CONH$; 5.12 (d, 3H) $NHCH(CO)CH_2$ and OCH_2Ph; 5.32 (d, 1H) NH; 6.71 (d, 1H) NH; 7.36 (s, 5H) Ph.

Z-Leu-DL-Nva-enol ester, the precursor of Z-Leu-DL-Nva-COOEt was synthesized by the same procedure as described in Example 1 and purified by column chromatography, oil, one spot on tlc. NMR ($CDCl_3$) d: 0.96 (t, 9H); 1.25 (t, 3H); 1.41 (t, 2H); 1.54 (m, 4H); 1.72 (m, 3H); 2.80 (t, 2H); 4.20 (q, 2H); 4.43 (q, 2H); 5.16 (q, 2H); 5.23 (s, 1H); 7.37 (m, 5H); 11.33 (s, 1H).

EXAMPLE 18

Z-Leu-DL-Phe-COOEt. This compound was prepared from Z-Leu-Phe-OH in 30 % yield by the procedure described in Example 1; oil, one spot on tlc, R_f = 0.47 ($CHCl_3$:MeOH = 50:1). NMR ($CDCl_3$) d: 0.88 (d, 9H), OCH_2CH_3 and $(CH_3)_2CH$; 1.35 (q, 2H), OCH_2CH_3; 1.56 (q, 2H), $(CH_3)_2CHCH_2CH$; 3.03 (m, 1H), $(CH_3)_2CH$; 4.32 (m, 2H), $NHCH(CO)CH_2$; 5.08 (s, 4H) CH_2Ph; 5.40 (m, 1H) NH; 6.61 (d, 1H) NH; 7.31 (s, 5H) Ph; 7.35.(s, 5H) Ph.

Z-Leu-DL-Phe-enol ester, the precursor of Z-Leu-DL-Phe-COOEt was synthesized by the same procedure as described in Example 1 and purified by column chromatography, oil, one spot on tlc. NMR ($CDCl_3$) d: 0.86 (t, 3H); 0.99 (t, 3H); 1.24 (t, 3H); 1.40 (t, 3H); 1.52 (m, 2H); 1.83 (m, 2H); 4.23 (m, 4H); 4.39 (q, 2H); 5.10 (t, 2H); 5.18 (s, 1H); 7.26 (m, 5H); 7.34 (m, 5H); 8.89 (s, 1H).

EXAMPLE 19

Z-Leu-DL-Abu-COOEt. This compound was prepared from Z-Leu-Abu-OH in 33 % yield by the procedure described in Example 1; oil, one spot on tlc, R_f = 0.66 ($CHCl_3$:MeOH = 20:1). NMR ($CDCl_3$) d: 0.96 (t, 9H), OCH_2CH_3 and $(CH_3)_2CH$: 1.26 (t, 3H), $CH_2CH_2CH_3$; 1.37 (q, 2H), OCH_2CH_3; 1.66 (q, 2H), $(CH_3)_2CHCH_2CH$; 2.00 (m, 1H), $CH(CH_3)_2$; 4.12 (q, 2H) $CHCH_2CH_3$; 4.34 (m, 1H) $NHCH(CONH)CH_2CH(CH_3)_2$; 5.12 (q, 3H) CH_2Ph and CONH(Et)CHCOCOO; 5.29 (t, 1H) NH; 6.79 (d, 1H) NH; 7.35 (s, 5H) Ph.

Z-Leu-DL-Abu-enol ester, the precursor of Z-Leu-DL-Abu-COOEt was synthesized by the same procedure as described in Example 1 and purified by column chromatography, oil,

one spot on tlc. NMR (CDCl3) d: 0.98 (t, 6H); 1.12 (t, 3H); 1.24 (t, 3H); 1.41 (t, 3H); 1.73 (m, 4H); 2.86 (q, 2H); 4.20 (q, 2H); 4.31 (m, 1H); 4.42 (q, 2H); 5.15 (q, 2H); 5.21 (s, 1H); 7.34 (m, 5H); 11.29 (s, 1H).

EXAMPLE 20

Ala-DL-Lys-COOEt·HCl. To a solution of N-carbobenzyloxyalanyl-Ne-carbobenzyloxylysine (1.88 g, 3.9 mmol), 4-dimethylaminopyridine (21 mg, 0.17 mmol), and pyridine (1.0 mL, 12.4 mmol) in THF (7 mL) was added ethyl oxalyl chloride (0.9 mL, 8.0 mmol) at a rate sufficient to start refluxing. The mixture was refluxed gently for 3 hr, treated with water (4 mL), and stirred vigorously at room temperature for 30 min. The mixture was extracted with ethyl acetate, the organic extracts were washed with water, dried over $MgSO_4$ and evaporated to give an oily residue (1.56 g). To a solution of the enol ester (1.56 g, 2.7 mmol) in anhydrous ethanol was added dropwise a solution of sodium ethoxide in ethanol at room temperature until the solution turned clear yellow. Ethanol was removed and the residue was dissolved in ethyl acetate. The organic solution was washed with water, dried over $MgSO_4$, and evaporated to give a residue. This residue was then purified by column chromatography and the product was eluted with chloroform-methanol. The solvent was removed and Z-Ala-DL-Lys(Z)-CO_2Et was obtained as a hygroscopic powder (328 mg, 16 %), single spot on tlc, R_f^2 = 0.53 ($CHCl_3$:MeOH = 9:1); MS, m/e = 542 (M^++1).

N-Carbobenzoxyalanyl-DL-Necarbobenzoxylysine keto ethyl ester, Z-Ala-DL-Lys(Z)-CO_2Et (328 mg, 0.61 mmol) was deprotected with liquid HF containing anisole at 0 °C for 30 min. The HF was removed under reduced pressure. The residual oil was dissolved in absolute ethanol. HCl/ethanol was added to the solution, and ethanol was removed in vacuo. The residue was washed by decantation with ether to give a semi solid (216 mg, 100 %); single spot on tlc (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2).

EXAMPLE 21

Bz-DL-Lys-COOEt·HCl. This compound was prepared from Bz-DL-Lys(Z)-COOEt in 62% yield by the procedure described in Example 20; one spot on tlc, R_f^4 = 0.57 (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2). The precursor, Bz-DL-Lys(Z)-COOEt was prepared from Bz-Lys(Z)-OH in 100% yield by the procedure described in Example 1; powder, one spot on tlc, R_f^2 = 0.75 ($CHCl_3$:MeOH = 9:1); MS, m/e = 440 (M^+). Anal. Calcd. for $C_{24}H_{28}O_6N_2 \cdot 2/3\ H_2O$: C, 63.70; H, 6.53; N, 6.19. Found: C, 63.49; H, 6.51; N, 5.92.

EXAMPLE 22

Bz-DL-Arg-COOEt·HCl. This compound was prepared from Bz-DL-Arg(Z)-COOEt in 99% yield by the procedure described in Example 20; one spot on tlc, R_f^4 = 0.71 (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2), Sakaguchi reagent positive. Bz-DL-Arg(Z)-COOEt was prepared from Bz-DL-Arg(Z)-OH in 19% yield by the procedure described in Example 20, R_f^2 = 0.38 ($CHCl_3$:MeOH = 9:1); mp 140-142 °C; MS, m/e = 468 (M^+). Anal. Calcd. for $C_{24}H_{28}O_6N_4$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.96; H, 6.48; N, 12.34.

EXAMPLE 23

H-Gly-DL-Lys-COOEt·2HCl. This compound was prepared from Z-Gly-DL-Lys(Z)-COOEt in 92% yield by the procedure described in Example 20; R_f^4 = 0.21 (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2). Z-Gly-DL-Lys(Z)-COOEt was prepared from Z-Gly-Lys(Z)-OH in 9% yield by the procedure described in Example 20, one spot on tlc, R_f^1 = 0.68 ($CHCl_3$:MeOH = 5:1); MS, m/e = 528 (M^++1).

EXAMPLE 24

H-Pro-DL-Lys-COOEt·2HCl. This compound was prepared from Z-Pro-DL-Lys(Z)-COOEt in 100% yield by the procedure described in Example 20; one spot on tlc (n-butanol:acetic acid:pyridine:H_2O = 4:1:1:2). Z-Pro-DL-Lys(Z)-COOEt was prepared from Z-Pro-Lys(Z)-OH in 15% yield by the procedure described in Example 20; R_f^2 = 0.73 (CHCl3:MeOH = 9:1); MS, m/e 568 (M^++1).

EXAMPLE 25

H-Phe-DL-Lys-COOEt·2HCl. This compound was prepared from Z-Phe-DL-Lys(Z)-COOEt in 39% yield by the procedure described in Example 20; one spot on tlc (n-butanol:acetic acid:pyridine:H2O = 4:1:1:2). Z-Phe-DL-Lys(Z)-COOEt was prepared from Z-Phe-Lys(Z)-OH as previously described in 9% yield, R_f^2 = 0.68 ($CHCl_3$:MeOH = 9:1); MS, m/e = 482 (M^+).

EXAMPLE 26

H-Leu-Ala-DL-Lys-COOEt·2HCl. This compound was prepared from Z-Leu-Ala-DL-Lys(Z)-COOEt in 52% yield by the procedure described in Example 20; one spot on tlc (n-butanol:acetic acid:pyridine:H2O = 4:1:1:2).

Z-Leu-Ala-DL-Lys(Z)-COOEt was prepared from Z-Leu-Ala-DL-Lys(Z)-OH in 5% yield by the previously described Dakin West reaction, R_f^3 = 0.34 ($CHCl_3$:MeOH = 19:1); MS, m/e = 609 (M^+-OCH2CH3).

EXAMPLE 27

Simple Amino Acid, Di- and Tripeptide Enol Esters (General Procedure). A modified Dakin-West procedure was used [Charles et al., *J. Chem. Soc. Perkin I*, 1139 (1980)] and is illustrated with the synthesis of Z-Leu-DL-Phe-EE. To a stirred solution of Z-Leu-Phe-OH (6.19 g, 15.0 mmol), 4-dimethylaminopyridine (0.183 g; 1.5 mmol) and pyridine (4.75 g, 4.85 ml, 60 mmol) in tetrahydrofuran (45 ml) warmed 50 °C was added ethyl oxalyl chloride (4.30 g, 3.52 ml, 31.5 mmol) at a rate sufficient to initiate refluxing. The mixture was then heated at a gentle reflux for 4 h. After cooling to room temperature the mixture was treated with water (25 ml) and stirred vigorously at room temperature for 30 min. The mixture was extracted with ethyl acetate (150 ml) and after separation of the organic layer, the water layer was saturated with solid $(NH_4)_2SO_4$ and re-extracted 2-times with 25 ml ethyl acetate. The combined organic phases were washed 2-times with 75 ml water, 2-times with 50 ml of satd. NaCl, decolorized with carbon and dried over $MgSO_4$. After evaporation of the solvent, the crude enol ester (8.36 g, 98%) was flash-chromatographed on silica gel and the product was

eluted with a AcOEt. The solvent was evaporated in vacuo (rotavaporator) and the pure enol ester was obtained as a oil (7.22 g, 85%); single spot on TLC, R_f = 0.84, A: 0.68, C.

Z-Leu-Nva-EE. This compound was prepared from Z-Leu-Nva-OH using the general procedure and purified by flash chromatography on silica gel using $CHCl_3$:MeOH = 50:1 v/v as eluent. Yield 95%, single spot on TLC, R_f = 0.92, C; 0.28 ,L.

Z-Leu-Abu-EE. This compound was prepared from Z-Leu-Abu-OH in 78% yield the general procedure described above. Purification by flash obramatography on silica gel. Eluent, $CHCl_3$:MeOH = 50:1 v/v, single spot on TLC, R_f = 0.86, A.

PhCO-Abu-EE. This compound was prepared from PhCO-Abu-OH in 26% yield by the general procedure as described above. Purification by flash chromatography on silica gel. Eluent $CHCl_3$, single spot on TLC, R_f = 0.60, M.

$(CH3)_2CH(CH_2)_2CO$-Abu-EE. This compound was prepared from $(CH_3)_2CH(CH_2)_2CO$-Abu-OH in 82% yield by the general procedure as described above. Purification by flash chromatography on silica gel. Eluent AcOEt, single spot on TLC, R_f = 0.72, C.

$(CH_3CH_2CH_2)_2$ CH CO-Abu-EE. This compound was prepared from $(CH_3CH_2CH_2)_2CH$ CO-Abu-OH in 100% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent AcOEt, single spot on TLC, R_f = 0.78, C; 0.81, K.

$Ph(CH_2)_6CO$-Abu-EE. This compound was prepared from $Ph(CH_2)_6CO$-Abu-OH in 86% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent AcOEt. Single spot on TLC, R_f =0.74, C.

Z-Leu-4-Cl-Phe-EE. This compound was prepared from Z-Leu-4-Cl-Phe-OH in 69% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent AcOEt, single spot on TLC, R_f = 0.77, C; 0.78, K.

Z-Leu-Leu-Abu-EE. This compound was prepared from Z-Leu-Leu-Abu-OH in 62% yield by the general procedure described above. Purification by flash chromatography on silica gel. Element $CHCl_3$:MeOH = 50:1 v/v. Single spot on TLC, R_f = 0.89, A; 0.75, M.

Z-Leu-Leu-Phe-EE. This compound was prepared from Z-Leu-Leu-Phe-OH in 60% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent $CHCl_3$:MeOH = 50:1 v/v. Single spot on TLC, R_f = 0.80, K; 0.70, M.

2-$NapSO_2$-Leu-Leu-Abu-EE. This compound was prepared from 2-$NapSO_2$-Leu-Abu-OH in 73% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent AcOEt, single spot on TLC, R_f = 0.71, K; 0.54, C.

2-$NapSO_2$-Leu-Leu-Abu-EE. This compound was prepared from 2-$NapSO_2$-Leu-Leu-Abu-OH in 74% yield by the general procedure described above. Purification by flash chromatography on silica gel. Eluent AcOEt: AcOH = 200:1 v/v. Single spot on TLC, R_f = 0.69, K.

Z-Leu-Phe-COOEt. *Single Aminoacid, Di-and Tripeptide-ketoesters (General Procedure).* To a stirred solution of 8.53 g (15.0 mmol) of Z-Leu-Phe-EE in 40 ml anhydrous ethanol at room temperature was added dropwise a solution of sodium ethoxide (0.204 g; 3.0 mmol) in 20.0 ml anhydrous ethanol. The color of the reaction mixture change from colorless or pale yellow to deep yellow or orange dependent on enol-ester. Then the reaction mixture was stirred at room temperature for 4-5 hours, the ethanol was then evaporated in vacuo (rotavaporator) and the residue treated with 200 ml ethyl ether (or 200 ml ethyl acetate in the case of the tripeptide). The ether (ethyl acetate) solution was washed with 2 x 75 ml H_2O, 2 x 75 ml satd. NaCl, decolorized with carbon and dried over $MgSO_4$. After evaporation of solvent, the crude product 6.09 g (89.7%) was flash chromatographed on silica gel using $CHCl_3$: MeOH = 50:1 v/v. Evaporation of solvent give pure Z-Leu-Phe-COOEt (4.08 g; 58.0%) as a thick oil. Single spot on TLC, R_f = 0.60, A; 0.47, M. Mass spectrum, FB-MS [(M+1)/Z] = 469.

EXAMPLE 28

2-Leu-Nva-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$: MeOH = 100:1 v/v, yield 86.6%, thick, colorless oil, single spot on TLC, R_f = 0.49, A; 0.37, M. Mass spectrum FB-MS [(M+1)/Z] = 421.

EXAMPLE 29

Z-Len-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$, yield 82%, thick, pale yellow oil, single spot on TLC, R_f = 0.66, A. Mass spectrum, CI-MS [(M+1)/Z] = 407.

EXAMPLE 30

PhCO-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50:1 v/v, yield 83%, oil, single spot on TLC, R_f = 0.44, M. Mass spectrum, M/Z 263 (M^+); CI-MS, 264 ((M+1)/Z).

EXAMPLE 31

$(CH_3)_2CH(CH_2)_2CO$-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent AcOEt, yield 43%, oil, single spot on TLC, R_f = 0.56, C. Mass spectrum EI-MS M/Z 257 (M^+); FB-MS, [(M+1)/Z] = 258.

EXAMPLE 32

$CH_3CH_2CH)_2CHCO$-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50: 1 v/v, thick, yellowish oil, yield 66%, single spot on TLC, R_f = 0.80, C; 0.66, M. Mass spectrum EI-MS M/Z = 285 (M^+); CI-MS, [(M+1)/Z] = 286.

EXAMPLE 33

$Ph(CH_2)_6CO$-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50:1 v/v, yield 64%, pale yellow oil, single spot on TLC, R_f = 0.29, M. Mass spectrum EI-MS M/Z = 347 (M^+), FB-MS, [(M+1)/Z] = 348.

EXAMPLE 34

Z-Leu-4-Cl-Phe-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent AcOEt, yield 100%, colorless oil, single spot on TLC, R_f = 0.71, C. Mass spectrum FB-MS M/Z = 503(M^+).

EXAMPLE 35

Z-Leu-Leu-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50:1 v/v, yield 79.2%, very thick, colorless oil, single spot on TLC, R_f = 0.28. M. Mass spectrum FB-MS, [(M+1)/Z] = 520.

EXAMPLE 36

Z-Leu-Leu-Phe-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50:1 v/v, yield 33%, oil, single spot on TLC, R_f = 0.56, M. Mass spectrum, FB-MS, [(M+1)/Z] = 582.

EXAMPLE 37

2-$NapSO_2$-Leu-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent $CHCl_3$:MeOH = 50:1 v/v, yield 38%, thick oil, single spot on TLC, R_f = 0.71, K; 0.54, A. Mass spectrum FB-MS, [(M+1)/Z] = 463.

EXAMPLE 38

2-$NapSO_2$-Leu-Leu-Abu-COOEt. This was prepared by the preceding general procedure. Purification by flash chromatography on silica gel, eluent AcOEt:AcOH = 200:1 v/v, yield 61%, semi-solid, single spot on TLC, R_f = 0.67, K. Mass spectrum FB-MS, [(M+1)/Z] = 576.

EXAMPLE 39

Z-Leu-Met-CO_2Et. This compound was prepared by the above procedure. Yellow oil, single spot on TLC, R_f = 0.52 ($CHCl_3$:CH_3OH=50:1), yield 46% (from dipeptide), MS (FAB) 454 (m+1).

EXAMPLE 40

Z-Leu-NLeu-CO_2Et. This compound was prepared by the above procedure. Pale yellow oil, single spot on TLC, R_f = 0.57 ($CHCl_3$:CH_3OH = 50:1), yield 53% (from dipeptide), MS (FAB) 434 (m+1).

EXAMPLE 41

Synthesis of n-Butyl Oxalyl Chloride: This was prepared by a literature procedure [Warren and Malee, *J. Chromat.* 64, 219-222 (1972)]. N-Butanol (0.1 mol. 7.41 g) was added dropwise to oxalyl chloride (0.5 mol. 63.5 g) at -10 °C. After the addition was

completed, the reaction mixture was stirred for 20 min. at r.t. and distilled, giving 15.0 g (91.18 mol. 91%) of the product n-butyl oxalyl chloride, bp 58-60 °C (0.6 mm Hg).

Z-Leu-Phe-CO_2Bu. This compound was prepared from Z-Leu-Phe-OH and butyl oxalyl chloride in 43% yield by the procedure described for the synthesis of Z-Leu-Phe-CO_2Et, except that butyl oxalyl chloride was used in place of ethyl oxalyl chloride and sodium butyloxide in butanol was used for enol ester hydrolysis. Single spot on TLC, R_f = 0.54 ($CHCl_3$:CH_3OH = 50:1) MS(FAB) m/e = 497 (m+1), ^1H NMR ($CDCl_3$) ok.

EXAMPLE 42

Z-Leu-Abu-CO_2Bu. This compound was prepared by the above procedure. Single spot on TLC, R_f = 0.53 ($CHCl_3$:CH_3OH = 50:1), yield = 36%, pale yellow oil, MS (FAB) m/e = 435 (M+1), ^1H NMR ($CDCl_3$) ok.

EXAMPLE 43

Synthesis of Benzyl Oxalyl Chloride. Benzyl alcohol (0.15 mol. 16 g) was added dropwise to oxalyl chloride (0.75 mol. 95 g) at 5-10 °C. After the addition was complete, the reaction was stirred for 20 min. at r.t. The excess oxalyl chloride was distilled and recycled. Then the mixture was distilled under vacuo, giving 26 g (0.12 mol. 86%) of benzyl oxalyl chloride, bp. 110-112 °C (0.6 mm-Hg). H^1NMR ($CDCl_3$) 7.39 (s, 5H), 5.33 (s, 2H).

Z-Leu-Phe-CO_2Bzl. This compound was prepared from Z-Leu-Phe-OH and benzyl oxalyl chloride in 17% yield by the procedure described in the synthesis of Z-Leu-Phe-CO_2Et, except that benzyl oxalyl chloride was used in place of ethyl oxalyl chloride and sodium benzyloxide in benzyl alcohol was used for enol ester hydrolysis. Single spot on TLC, R_f = 0.63 ($CHCl_3$:CH_3OH = 50:1). Pale yellow solid, mp 117-119 °C. MS(FAB) m/e = 532 (m+1). H^1NMR ok.

EXAMPLE 44

Z-Leu-Abu-CO_2Bzl. This compound was prepared by the above procedure. Single spot on TLC. R_f = 0.51 ($CHCl_3$:CH_3OH = 50:1), pale yellow oil, MS(FAB) m/e = 469 (m+1), yield = 26%.

EXAMPLE 45

Z-Leu-Phe-COOH. Dipeptide Ketoacids (General Procedure). To a stirred solution of 0.53g (1.13 mmol) Z-Leu-Phe-COOEt in 6.0 ml methanol was added 1.27 ml (1.27 mmol) 1M NaOH. The color of the reaction mixture turned dark yellow and a small amount of solid was deposited. The reaction was run at room temperature and progress of the hydrolysis was checked on TLC. After 24 h. no more substrate was detected. The reaction mixture was chilled in one ice bath at 5 °C, acidified with 1M HCl to pH = 3 and extracted with AcOEt (2 x 50 mL). The organic extract were washed with 2 x 50 ml H_2O and if necessary, decolorized with carbon and dried over $MgSO_4$. After evaporation of the solvent (rotavaporator), the residue (thick oil) were titurated with 2 x 25 ml n-hexane and dried in vacuo. Yield 0.39 g (78%) of colorless, very thick oil. TLC, main spot at R_f = 0.24, trace of impurity at R_f = 0.78, I. Mass spectrum, FB-MS [(M+1)/Z] = 441.

EXAMPLE 46

Z-Leu-Abu-COOH. This compound was prepared from Z-L-Leu-Abu-COOEt in 83% yield by the general procedure as described above; TLC, main spot at $R_f = 0.14$, trace of impurity at $R_f = 0.73$, I. Mass spectrum, FB-MS [(M+1)/Z] = 379.

Example 47

Z-Leu-Phe-CONH-Et. To a stirred solution of Z-Leu-Phe-OH (20 g, 48.5 mmole), 4-dimethylaminopyridine (0.587 g, 4.8 mmole),and pyridine (15.7 ml, 194 mmole) in anhydrous THF (100 ml) was added ethyl oxalyl chloride (11.4 ml, 101.8 mmole) at a rate sufficient to initiate refluxing. The mixture was gently refluxed for 4 hours, cooled to room temperature, and water (80 ml) was added. The reaction mixture was stirred vigorously for 30 min, and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (2 x 100 ml), saturated sodium chloride (2 x 100 ml), decolorized with decolorizing carbon, dried over magnesium sulfate, and concentrated, leaving a dark orange oil. Chromatography on a silica gel column with $CHCl_3/CH_3OH$ (50:1 v/v) afforded 14.63 g (y = 53 %) of Z-Leu-Phe-enolester. The product was a yellow oil. Single spot on TLC, $R_f = 0.77$ ($CHCL_3/CH_3OH$ 50:1). NMR ($CDCl_3$) ok.

To a stirred pale yellow solution of the Z-Leu-Phe-enolester (14.63 g, 25.73 mmole) in anhydrous ethanol (50 ml) was added a solution of sodium ethoxide (0.177 g, 2.6 mmole) in ethanol (5 ml). The orange solution was stirred for 3 hours at room temperature, then the ethanol was evaporated and the residue was treated with ethyl ether (300 ml). The ether layer was washed with water (2 x 100 ml), saturated sodium chloride (2 x 100 ml), dried over magnesium sulfate, and concentrated, leaving a orange oil. Chromatography on a silica gel column with $CHCl_3/CH_3OH$ (50:1 v/v) afforded 7.76 g (y = 64 %) of the α-ketoester Z-Leu-Phe-COOEt. The product was a yellow oil. Single spot on TLC, $R_f = 0.44$ ($CHCl_3/CH_3OH$ 50:1). NMR ($CDCl_3$) ok. MS (FAB, calcd. for $C_{26}H_{32}N_2O_6$: 468.6), m/e = 469 (M+1).

The α-carbonyl group of Z-Leu-Phe-COOEt was protected by following procedure. A solution of Z-Leu-Phe-COOEt (1 g, 2.13 mmole) in 5 ml of CH_2Cl_2 was added 1,2-ethanedithiol (0.214 ml, 2.55 mmole), followed by 0.5 ml of boron trifluoride etherate. The solution was stirred overnight at room temperature. Water (20 ml) and ethyl ether (20 ml) were added. The organic layer was separated, washed with water (2 x 10 ml), saturated sodium chloride (2 x 10 ml), dried over magnesium sulfate, and evaporated to afford 0.98 g (y = 84 %) yellow semisolid.

The protected α-ketoester (0.98 g, 1.8 mmole) was dissolved in ethanol (5 ml), cooled to 0-5 °C in a ice bath, and ethylamine was bubbled through the solution until 2.43 g (54 mmole) had been added. The reaction mixture was allowed to warm to room temperature slowly, and stirred overnight. The mixture was filtered, a white precipitate was removed, leaving a yellow semisolid. Chromatography on a silica gel column with $CHCl_3/CH_3OH$ (30:1 v/v) afford 0.63 g (y = 75 %) of Z-Leu-Phe-CONH-Et. The product was a pale yellow solid. Single spot on TLC, $R_f = 0.60$ ($CHCl_3/CH_3OH$ 20:1); mp 145-147 °C. Anal. calcd. for

$C_{26}H_{33}N_3O_5$: 467.56; C, 66.79; H, 7.11; N,8.99; found: C, 66.59; H, 7.09; N, 8.95. NMR ($CDCl_3$) ok. MS (FAB) m/e = 468 (M+1).

Example 48

Z-Leu-Phe-CONH-nPr. This compound was synthesized from the protected α-ketoester and propylamine in 92 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.50 ($CHCl_3/CH_3OH$ 50:1); mp 152-153 °C. Anal. calcd. for $C_{27}H_{35}N_3O_5$: 481.57; C, 67.33; H, 7.33; N, 8.72. Found: C, 67.21; H, 7.38; N, 8.64. NMR ($CDCl_3$) ok. MS (FAB) m/e = 482 (M+1).

Example 49

Z-Leu-Phe-CONH-nBu. This compound was synthesized from the protected α-ketoester and butylamine in 67 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.50 ($CHCl_3/CH_3OH$ 50:1); mp 152-153 °C. Anal. calcd. for $C_{28}H_{37}N_3O_5$: 495.59; C, 67.85; H, 7.52; N, 8.48. Found: C, 67.70; H, 7.57; N, 8.43. NMR ($CDCl_3$) ok. MS (FAB) m/e = 496 (M+1).

Example 50

Z-Leu-Phe-CONH-iBu. This compound was synthesized from the protected α-ketoester and isobutylamine in 53 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.54 ($CHCl_3/CH_3OH$ 50:1); mp 152 °C. Anal. calcd. for $C_{28}H_{37}N_3O_5$: 495.59; C, 67.85; H, 7.52; N, 8.48. Found: C, 67.77; H, 7.56; N, 8.40. NMR ($CDCl_3$) ok. MS (FAB) m/e = 496 (M+1).

Example 51

Z-Leu-Phe-CONH-Bzl. This compound was synthesized from the protected α-ketoester and benzylamine in 40 % yield by the procedure described in Example 47. After reacting overnight, ethyl acetate (60 ml) was added. The mixture was filtered to remove a white precipitate. The solution was washed with cooled 1 N HCl (3 x 25 ml), water (1 x 20 ml), saturated sodium chloride (2 x 20 ml), and dried over magnesium sulfate. The solution was evaporated leaving a yellow solid. Chromatography on a silica gel column with $CHCl_3/CH_3OH$ 30:1 v/v) afforded a yellow solid. Single spot on TLC, R_f = 0.45 ($CHCl_3/CH_3OH$ 30:1); mp 160-162 °C. Anal. calcd. for $C_{31}H_{35}N_3O_5$: 529.61; C, 70.30; H, 6.66; N, 7.93. Found: C, 70.18; H, 6.67; N, 7.99. NMR ($CDCl_3$) ok. MS (FAB) m/e = 530 (M+1).

Example 52

Z-Leu-Phe-CONH-$(CH_2)_2$Ph. This compound was synthesized from the protected α-ketoester and phenethylamine in 50 % yield by the procedure described in Example 51. Single spot on TLC, R_f = 0.50 ($CHCl_3/CH_3OH$ 30:1); mp 151-153 °C. Anal. calcd. for $C_{32}H_{37}N_3O_5$: 543.66; C, 70.70; H, 6.86; N, 7.73. Found: C, 70.54; H, 6.88; N, 7.74. NMR ($CDCl_3$) ok. MS (FAB) m/e = 544 (M+1).

Example 53

Z-Leu-Abu-CONH-Et. This compound was synthesized from protected α-ketoester derived from Z-Leu-Abu-CO_2Et and ethylamine in 64 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.36 ($CHCl_3/CH_3OH$ 50:1); mp 130-132 °C. Anal. calcd. for $C_{21}H_{31}N_3O_5$: 405.45; C, 62.20; H, 7.71; N, 10.36. Found: C, 61.92; H, 7.62; N, 10.31. NMR ($CDCl_3$) ok. MS (FAB) m/e = 406 (M+1).

Example 54

Z-Leu-Abu-CONH-nPr. This compound was synthesized from the corresponding protected α-ketoester and propylamine in 47 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.28 ($CHCl_3/CH_3OH$ 50:1); mp 134-135 °C. Anal. calcd. for $C_{22}H_{33}N_3O_5$: 419.50; C, 62.98; H, 7.93; N, 10.02. Found: C, 62.84; H, 7.97; N, 9.94. NMR ($CDCl_3$) ok. MS (FAB) m/e = 420 (M+1).

Example 55

Z-Leu-Abu-CONH-nBu. This compound was synthesized from the corresponding protected α-ketoester and butylamine in 42 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.54 ($CHCl_3/CH_3OH$ 50:1); mp 135-136 °C. Anal. calcd. for $C_{23}H_{35}N_3O_5$: 433.53; C, 63.71; H, 8.13; N, 9.69. Found: C, 63.48; H, 8.07; N, 9.67. NMR ($CDCl_3$) ok. MS (FAB) m/e = 434 (M+1).

Example 56

Z-Leu-Abu-CONH-iBu. This compound was synthesized from the corresponding protected α-ketoester and isobutylamine in 65 % yield by the procedure described in Example 47. Single spot on TLC, R_f = 0.25 ($CHCl_3/CH_3OH$ 50:1); mp 133-135 °C. Anal. calcd. for $C_{23}H_{35}N_3O_5$: 433.52; C, 63.72; H, 8.14; N, 9.69. Found: C, 63.46; H, 8.10; N, 9.60. NMR ($CDCl_3$) ok. MS (FAB) m/e = 434 (M+1).

Example 57

Z-Leu-Abu-CONH-Bzl. This compound was synthesized from the corresponding protected α-ketoester and benzylamine in 29 % yield by the procedure described in Example 51. Single spot on TLC, R_f = 0.56 ($CHCl_3/CH_3OH$ 30:1); mp 140-141 °C. Anal. calcd. for $C_{26}H_{33}N_3O_5$: 467.54; C, 66.79; H, 7.11; N, 8.99. Found: C, 66.65; H, 7.07; N, 8.93. NMR ($CDCl_3$) ok. MS (FAB) m/e = 468 (M+1).

Example 58

Z-Leu-Abu-CONH-$(CH_2)_2$Ph. This compound was synthesized from the corresponding protected α-ketoester and phenethylamine in 51 % yield by the procedure described in Example 51. Single spot on TLC, R_f = 0.44 ($CHCl_3/CH_3OH$ 30:1); mp 156-157 °C. Anal. calcd. for $C_{27}H_{35}N_3O_5$: 481.59; C, 67.34; H, 7.33; N, 8.72. Found: C, 67.38; H, 7.33; N, 8.78. NMR ($CDCl_3$) ok. MS (FAB) m/e = 482 (M+1).

Example 59

Z-Leu-Abu-CONH-$(CH_2)_3$-N$(CH_2CH_2)_2$O. This compound was synthesized from protected α-ketoester and 4(3-aminopropyl)morpholine in 33 % yield by the procedure described in Example 47. After reacting overnight, ethyl acetate (80 ml) was added. The

mixture was filtered to remove a white precipitate. The solution was washed with water (3 x 20 ml), saturated sodium chloride (2 x 20 ml), and dried over magnesium sulfate. The solution was evaporated leaving a yellow oil. Chromatography on a silica gel column with $CHCl_3/CH_3OH$ (10:1 v/v) afforded a yellow semisolid, which was recrystallized from ethyl acetate/hexane to obtain a pale yellow solid. Single spot on TLC, $R_f = 0.42$ ($CHCl_3/CH_3OH$ 10:1); mp 125-126 °C. Anal. calcd. for $C_{26}H_{40}N_4O_6$: 504.63; C, 61.88; H, 7.99; N, 11.10. Found: C, 61,69; H, 7.95; N, 11.07. NMR ($CDCl_3$) ok. MS (FAB) m/e = 505 (M+1).

Example 60

Z-Leu-Abu-CONH-$(CH_2)_7CH_3$. This compound was synthesized from the corresponding protected α-ketoester and octylamine in 67 % yield by the procedure described in Example 51. It was white solid. Single spot on TLC, $R_f = 0.55$ ($CHCl_3/CH_3OH$ 30:1); mp 134-135 °C. Anal. calcd. for $C_{27}H_{43}N_3O_5$: 489.66; C, 66.23; H, 8.85; N, 8.58. Found: C, 66.19; H, 8.81; N, 8.61. NMR ($CDCl_3$) ok. MS (FAB) m/e = 490 (M+1).

Example 61

Z-Leu-Abu-CONH-$(CH_2)_2OH$. This compound was synthesized from the corresponding protected α-ketoester and ethanolamine in 29 % yield by the procedure described in Example 59. The product was a white sticky solid. Single spot on TLC, $R_f = 0.42$ ($CHCl_3/CH_3OH$ 10:1); mp 151-153 °C. Anal: calcd. for $C_{21}H_{31}N_3O_6$: 421.49; C, 59.84; H, 7.41; N, 9.97. Found: C, 59.11; H, 7.44; N, 9.81. NMR ($CDCl_3$) ok. MS (FAB) m/e = 422 (M+1).

Example 62

Z-Leu-Abu-CONH-$(CH_2)_2O(CH_2)_2OH$. This compound was synthesized from the corresponding protected α-ketoester and 2-(2-aminoethoxy)ethanol in 34 % yield by the procedure described in Example 59. The product was white sticky solid. Single spot on TLC, $R_f = 0.42$ ($CHCl_3/CH_3OH$ 10:1); mp 103-105 °C. Anal.: calcd. for $C_{23}H_{35}N_3O_7$: 465.55; C, 59.34; H, 7.58; N, 9.03. Found: C, 59.23; H, 7.58; N, 9.01. NMR ($CDCl_3$) ok. MS (FAB) m/e = 466 (M+1).

Example 63

Z-Leu-Abu-CONH-$(CH_2)_{17}CH_3$. This compound was synthesized from the corresponding protected α-ketoester and octadecylamine in 12 % yield by the procedure described in Example 51. The product was a pale yellow solid. Single spot on TLC, $R_f =$ 0.54 ($CHCl_3/CH_3OH$ 30:1); mp 134-136 °C. Anal: calcd. for $C_{37}H_{63}N_3O_5$: 629.92; C, 70.55; H, 10.08; N, 6.67. Found: C, 70.71; H, 10.14; N, 6.75. NMR ($CDCl_3$) ok. MS (FAB) m/e = 630.2 (M+1).

Example 64

Z-Leu-Abu-CONH-CH_2-$C_6H_3(OCH_3)_2$. This compound was synthesized from the corresponding protected α-ketoester and 3,5-dimethoxybenzylamine in 45 % yield by the procedure described in Example 51. The product was yellow sticky solid. Single spot on TLC, $R_f = 0.44$ ($CHCl_3/CH_3OH$ 30:1); mp 153-155 °C. Anal.: calcd. for $C_{28}H_{37}N_3O_7$:

527.62; C, 63.74; H, 7.07; N, 7.96. Found: C, 63.66; H, 7.09; N, 7.92. NMR ($CDCl_3$) ok. MS (FAB) m/e = 528.8 (M+1).

Example 65

Z-Leu-Abu-CONH-CH_2-C_4H_4N. This compound was synthesized from the corresponding protected α-ketoester and 4-(aminomethyl)pyridine in 45 % yield by the procedure described in Example 59. The product was greenish yellow solid. Single spot on TLC, R_f = 0.55 ($CHCl_3$/CH_3OH 10:1); mp 124-126 °C. Anal: calcd. for $C_{25}H_{32}N_4O_5$: 468.55; C, 64.08; H, 6.88; N, 11.96. Found: C, 63.88; H, 6.87; N, 11.96. NMR ($CDCl_3$) ok. MS (FAB) m/e =469 (M+1).

It is obvious that those skilled in the art may make modifications to the invention without departing from the spirit of the invention or the scope of the subjoined claims and their equivalents.

Table I. Inhibition of serine proteases by peptide ketoesters and ketoacids.[a]

Compounds	K_I (μM)			
	HLE	PPE	Cathepin G	Chymotrypsin
Bz-DL-Phe-COOEt			58	0.28
Bz-DL-Ala-COOEt	640	590		
Bz-DL-Ala-COOH	3100	3200		
Bz-DL-Ala-COOBzl	19	23		
Bz-DL-Ala-COO-*n*-Bu	260	NI[b]		
Bz-DL-Ala-$COOCH_2$-C_6H_4-CF_3 (para)	81[c]	11[c]		
Z-Ala-DL-Ala-COOEt	100	210		
Z-Ala-DL-Ala-COO-*n*-Bu	250	80		
Z-Ala-DL-Ala-COOBzl	46	11		
MeO-Suc-Ala-DL-Ala-COOMe	470[c]	520[c]		
Z-Ala-Ala-DL-Ala-COOEt	1.3	0.65		
Z-Ala-Ala-DL-Nva-COOEt	0.52	0.36		
Z-Ala-Pro-DL-Ala-COOEt	2.8	2.4		
Z-Ala-Ala-DL-Abu-COOEt	0.12	0.15		
Z-Ala-Ala-DL-Abu-COOBzl	0.09	0.08		
Z-Ala-Ala-DL-Abu-$COOCH_2$-C_6H_4-CF_3 (para)	0.08	0.33		
MeO-Suc-Val-Pro-DL-Phe-COOMe			1.1	0.26
Z-Ala-Ala-Ala-DL-Ala-COOEt	0.3	0.14		
MeO-Suc-Ala-Ala-Pro-DL-Abu-COOMe	0.42	0.93		

[a]Inhibition constants were measured in 0.1 M Hepes, 0.5 M NaCl, pH 7.5 buffer, 9 % Me_2SO and at 25 °C.

[b]No inhibition.

[c]Noncompetitive inhibition.

Table II. Inhibition of serine proteases by peptide ketoesters and ketoacids.[a]

Compounds	K_I (μM)					
	Bovine Trypsin	Bovine Thrombin	Human Plasma Kallikrein	Porcine Pancreatic Kallikrein	Human Factor XIa	Human Plasmin
Bz-DL-Arg COOEt	58[b]	48[b]	>240	>240	38[c]	14[b]
Bz-DL-Lys-COOEt	1.6[d]	>240	76[b]	>140	140[b]	
H-Gly-DL-Lys-COOEt	4.1[d]	31	120	>140		
H-Ala-DL-Lys-COOEt	2.8[d]		>240	NI[e]		
H-Pro-DL-Lys-COOEt	3.4[d]		>270	>270		
H-Phe-DL-Lys-COOEt	17[d]		>120	NI		
H-Leu-Ala-DL-Lys-COOEt	16[d]		>180	>140		

[a]Inhibition constants were measured in 0.1 M Hepes, 10 mM $CaCl_2$, pH 7.5 buffer, 5.6-8.8 % Me_2SO and at 25 °C. Z-Arg-SBzl or Z-Gly-Arg-SBu-i were used as substrates.

[b]Competitive inhibition.

[c]Uncompetitive inhibition.

[d]Enzyme and inhibitor was preincubated before addition of the substrate.

[e]No inhibition at 120-240 μM.

Table III. Inhibition of cysteine proteases by peptide ketoesters and ketoacids.

Compounds	K_I (μM)			
	Papain[a]	Cathepsin B[b]	Calpain I[c]	Calpain II[c]
Z-Leu-Abu-COOEt			0.04	0.4
Z-Leu-Phe-COOEt			0.23	0.4
Z-Leu-Nle-COOEt			0.12	0.18
Bz-DL-Phe-COOEt	500[d]	64		
Z-Phe-DL-Phe-COOEt	1.8	0.1		
Z-Phe-DL-Ala-COOEt	3.6	3.2		
Z-Ala-Ala-DL-Ala-COOEt	1.5	2.2	200	
Z-Ala-Ala-DL-Abu-COOEt	0.9	10	50	200
Z-Ala-Ala-DL-Abu-COOBzl	30	60		
Z-Ala-Ala-DL-Nva-COOEt	30	0.1		
Z-Ala-Pro-DL-Ala-COOEt	26	66		
MeO-Suc-Val-Pro-DL-Phe-COOMe	1.1 2.9[d]	0.1		
Z-Ala-Ala-Ala-DL-Ala-COOEt	2.1	10.0		
MeO-Suc-Ala-Ala-Pro-Abu-COOMe	0.7	6.0	100	

[a]Inhibition constants were measured in 0.05 M Tris·HCl, pH 7.5 buffer , containing 2 mM EDTA, 5 mM cysteine (freshly prepared), 1 % Me_2SO, and at 25 °C. N^{α}-Benzoyl-Arg-AMC was used as a substrate.

[b]Inhibition constants were measured in 88 mM KH_2PO4, 12 mM Na_2HPO4, pH 6.0 buffer , containing 1.33 mM EDTA, 2.7 mM cysteine (freshly prepared), and at 25 °C. Z-Arg-Arg-AFC was used as a substrate.

[c]Inhibition constants were measured in 20 mM Hepes, pH 7.2 buffer , containing 10 mM $CaCl_2$, 10 mM β-mercaptoethanol, and at 25 °C. Suc-Leu-Tyr-AMC was used as a substrate.

[d]Inhibition constants were measured in 50 mM Tris·HCl, pH 7.5 buffer , containing 20 mM EDTA, 5 mM cysteine, 9 % Me_2SO, and at 25 °C. N^{α}-Benzoyl-Arg-NA was used as a substrate.

Table IV. Inhibition of Calpain I, Calpain II, Cathepsin B, PP Elastase, Papain, Platelets by Peptide Ketoamides, Ketoesters, and Ketoacids. Stability in Plasma and in Liver.

Inhibitor	K_I (uM)								
	Calpain I	Calpain II	CathB	Chym	elastase	papain	platelet	t1/2 plasma	t1/2 liver
Z-Leu-Abu-COOEt	4.5	0.4	30	>100	>100	220	42	2.8	
Z-Leu-Abu-COOnBu	1.8		4	>100	25	10	28		
Z-Leu-Abu-COOBz	9.5	0.47	4	40	>100	40	++		
Z-Leu-Leu-Abu-COOEt	1.8	2.6	22	>100	25		40		
2-NapSO_2-Leu-Leu-Abu-COOEt	16	1.4	25	35	47		100	>60	
2-NapCO-Leu-Leu-Abu-COOEt		0.09		>300	28			25	
Tos-Leu-Leu-Abu-COOEt	33		69	25	28		30	30	
Ph-$(CH_2)_2$-CO-Leu-Abu-COOEt		1.2							
Ph-$(CH_2)_3$-CO-Leu-Abu-COOEt									
Z-Leu-Abu-COOH	0.075	0.022	1.5	>150	>150		8	>60	>60
Z-Leu-Abu-CONHEt	0.5	0.23	2.4	>150	65		1.5	>60	>60
Z-Leu-Abu-CONHnPr		0.25	8	>300	2		70	>60	>60
Z-Leu-Abu-CONHnBu	0.2		13	>300	5		2.0	>60	>60
Z-Leu-Abu-CONHiBu		0.14	4	>300	40		28	>60	
Z-Leu-Abu-CONHBz		0.35	2	>300			1.5	>60	>60
Z-Leu-Abu-CONH-$(CH_2)_2$-Ph		0.022							
Z-Leu-Abu-CONH-$(CH_2)_3$-Mpl		0.041							
Z-Leu-Abu-CONH-$(CH_2)_7CH_3$		0.019							
Z-Leu-Abu-CONH-$(CH_2)_{17}CH_3$									
Z-Leu-Abu-CONH-$(CH_2)_2OH$		0.078							

Table IV (Continued). Inhibition of Calpain I, Calpain II, Cathepsin B, PP Elastase, Papain, Platelets by Peptide Ketoamides, Ketoesters, and Ketoacids. Stability in Plasma and in Liver.

Inhibitor	K_I (uM)								
	Calpain I	Calpain II	CathB	Chym	elastase	papain	platelet	t1/2	t1/2
Z-Leu-Abu-CONH-$(CH_2)_2O(CH_2)_2OH$	0.16								
Z-Leu-Phe-COOEt	1.8	0.4	340	0.05	>100	75	42	7.8	
Z-Leu-Phe-COOnBu	5.0	1.1	15	0.15	>100	15	+++	7.7	
Z-Leu-Phe-COOBz	3.4	1.6	45	1.6	>100	45	++	1.9	
Z-Leu-Leu-Phe-COOEt	1.4	1.9	42	0.26	>100	15	++		
Z-Leu-Phe-COOH	0,0085	0.0057	4.5	76	>150		6.5	>60	>60
Z-Leu-Phe-CONHEt	7.0	0.32	6	73	>150		1.7	>60	>60
Z-Leu-Phe-CONHnPr	15.0	0.05	3	18	>300		24	>60	>60
Z-Leu-Phe-CONHnBu		0.028	3	8	>100		38	>60	>60
Z-Leu-Phe-CONHiBu		0.065	4	24			22	>60	
Z-Leu-Phe-CONHBz		0.046							
Z-Leu-Phe-CONH$(CH_2)_2$Ph		0.024		(2)			3.0	>60	
Z-Leu-Nle-COOEt		0.18	20		2.2	190	20	3.7	
Z-Leu-Nva-COOEt	1.4	1.2	25	160	2.3	150	40	2.8	
Z-Leu-Met-COOEt	1.0	1.5	55	1.75	>100	140	+	8	
Z-Leu-4-Cl-Phe-COOEt	<4.0	0.4	50	0.9	>100	150	+		

(+++ = excellent activity; ++ = good activity, + = moderate activity; quantitiative measurements not yet complete)

What is claimed is:

1. A compound of the formula:

M_1-AA-NH-CHR_2-CO-CO-NR_3R_4

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 is selected from the group consisting of C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, and C_{1-8} branched and unbranched fluoroalkyl;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an

attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

2. A compound of the formula:

$$M_1\text{-}AA_2\text{-}AA_1\text{-}CO\text{-}NR_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-

cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

3. A compound of the formula:

$$M_1\text{-AA-AA-AA-CO-NR}_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

4. A compound of the formula:

$$M_1\text{-AA-AA-AA-AA-CO-NR}_3\text{R}_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H. NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

5. A compound of the formula:

M_1-AA-CO-NR_3R_4

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20}

alkyl with an OH group attached to the alkyl, $-CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

6. A compound of the formula:

$$M_1\text{-AA-NH-CHR}_2\text{-CO-CO-OH}$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

7. A compound of the formula:

M_1-AA_2-AA_1-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-

ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH. NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

8. A compound of the formula:

M_1-AA-AA-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH. NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

9. A compound of the formula:

M_1-AA-AA-AA-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y_1-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y_1 is selected from the group consisting of C_{2-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

10. A compound of the formula:

M_1-AA-CO-OH

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y_2-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y_2 is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

11. A compound of the formula:

$$M_1\text{-}AA_2\text{-}AA_1\text{-CO-O-}R_1$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-

cyclopentyl)-COOH. NH_2-CH(CH_2-cyclobutyl)-COOH. NH_2-CH(CH_2-cyclopropyl)-COOH. trifluoroleucine, and hexafluoroleucine;

R_1 is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

12. A compound of the formula:

M_1-AA-NH-CHR_2-CO-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH. NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH. NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

13. A compound of the formula:

M_3-AA-AA-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid,

NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{2-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

14. A compound of the formula:

M_3-AA-AA-NH-CHR_2-CO-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{1-10} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine,

homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 represents C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, or C_{1-8} branched and unbranched fluoroalkyl;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

15. A compound of the formula:

M_3-AA_4-AA-AA-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_3 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, T-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

T is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{2-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;;

AA_4 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of leucine, isoleucine, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

16. A compound of the formula:

M_1-AA-CO-O-R

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, Y-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

Y is selected from the group consisting of C_{6-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, and C_{1-10} alkyl with two attached phenyl groups substituted with K;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, $C_{1-C_{10}}$ acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R is selected from the group consisting of H, C_{1-20} alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, and C_{1-20} alkyl with an attached phenyl group substituted with K.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09801

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 265/30, 211/70; C07C 229/00, 233/00

U.S. CL: 544/168; 546/336; 562/561; 564/152, 153,154,155,158,159

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U. S.	544/168; 546/336; 562/561; 564/152, 153, 154, 155, 158, 159

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Substructure search in registry file of CAS data base.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4,820,691 (PATEL) 11 APRIL 1989 See entire document.	1, 2
A	EP, A, 0,195,212 (KULB) 24 SEPTEMBER 1986 pages 1-55, (Note pages 2 and 3).	1, 2
A	Archives of Biochemistry and Biophysics, Vol. 281, No. 2, September 1990, Lain-Yen Hu, "Inhibition of Cathepsin Band Papain by Peptidyl -Keto Esters, -Keto Amides, -Diketones, and -Keto Acids" pages 271-274 (note Table I on page 272).	1, 2

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

30 MARCH 1992

Date of Mailing of this International Search Report

22 APR 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

MICHAEL L. SHIPPIN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

SEE ATTACHMENT

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

Claims 1 and 2 to the extent they read on Group CLXXXIII as set forth in the listing of multiple inventions above.

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE FIRST SHEET
(Not for publication)

Attachment of Form PCT/ISA/210, PartVI

Sheet 1

Claims 1-16 read on a diversity of distinct inventions depending upon the structure of the compounds being claims. In general the claims read on compounds of the formula

$$M-(AA)_n-CO-R.$$

Distinct inventions are represented by compounds of

A. Groups I-XXVI wherein n=1, R=NR_1R_2. AA is a heterocyclic amino acid and

I. M is hydrogen.

II. M is $X_2-N-CG-$ (wherein X is H or acyclic and G is O or S).

III. M is " (wherein at least one X is alkanyl and the other X is alkanyl or as defined in Group I and G is O or S).

IV. M is " (wherein at least one X is fluoroalkyl and the other X is fluoroalkyl or as defined in Groups I or II and G is O or S).

V. M is " (wherein at least one X is aryl or aryl substituted alkyl and the other X is aryl or aryl substituted alkyl or as defined in Groups I, II or III and G is O or S).

VI. M is " (wherein at least one X is aryloxy or aryloxy substituted alkyl and the other X is aryloxy or aryloxy substituted alkyl or as defined in Groups I, II, III or IV and G is O or S).

VII. M is X_2-N-SO_2- (wherein X is H or acyclic).

VIII. M is " (wherein at least one X is alkanyl and the other X is alkanyl or as defined in Group I).

IX. M is " (wherein at least one X is fluoroalkyl and the other X is fluoroalkyl or as defined in Groups I or II).

X. M is " (wherein at least one X is aryl or aryl substituted alkyl and the other X is aryl or aryl substituted alkyl or as defined in Groups I, II or III).

XI. M is " (wherein at least one X is aryloxy or aryloxy substituted alkyl and the other X is aryloxy or aryloxy substituted alkyl or as defined in Groups I, II, III or IV).

Attachment of Form PCT/ISA/210, Part VI

Sheet 2

XII. M is X-CG- (wherein I is H or acyclic and G is O or S),

XIII. M is " (wherein I is adamantyl and G is O or S),

XIV. M is " (wherein I is fluorenyl and G is O or S),

XV. M is " (wherein I is aryl or aryl substituted alkyl and G is O or S),

XVI. M is " (wherein I is aryloxy or aryloxy substituted alkyl and G is O or S),

XVII. M is X-SO_2- (wherein I is H or acyclic),

XVIII. M is " (wherein I is adamantyl),

XIX. M is " (wherein I is fluorenyl),

XX. M is " (wherein I is aryl or aryl substituted alkyl),

XXI. M is " (wherein I is aryloxy or aryloxy substituted alkyl),

XXII. M is X-O-CG- (wherein I is H or acyclic and G is O or S),

XXIII. M is " (wherein I is adamantyl and G is O or S),

XXIV. M is " (wherein I is fluorenyl and G is O or S),

XXV. M is " (wherein I is aryl or aryl substituted alkyl and G is O or S),

XXVI. M is " (wherein I is aryloxy or aryloxy substituted alkyl and G is O or S),

B. Groups XXVII-LII wherein n=1, R=NR_3R_4, AA is an aromatic amino acid and M is as defined in Groups I-XXVI respectively.

C. Groups LIII-LXXVIII wherein n=1, R=NR_3R_4, AA is a cyclic amino acid and M is as defined in Groups I-XXVI respectively.

D. Groups LXXIX-CIV wherein n=1, R=NR_3R_4, AA is an acyclic amino acid and M is as defined in Groups I-XXVI respectively,

E. Groups CV-CXXX wherein n=2, R=NR_3R_4, at least one AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively,

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F. Groups CXXXI-CLVI wherein n=2. $R=NR_1R_4$, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

G. Groups CLVII-CLXXXII wherein n=2, $R=NR_1R_4$, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-XXVI respectively,

H. Groups CLXXXIII-CCVIII wherein n=2. $R=NR_1R_4$. AA is an acyclic amino acid and the other AA is not heterocyclic, aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

I. Groups CCIX-CCXXXIV wherein n=3, $R=NR_1R_4$, at least one AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively,

J. Groups CCXXXV-CCLX wherein n=3, $R=NR_1R_4$, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

K. Groups CCLXI-CCLXXXVI wherein n=3, $R=NR_1R_4$, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-XXVI respectively,

L. Groups CCLXXXVII-CCCXII wherein n=3, $R=NR_1R_4$, at least one AA is an acyclic amino acid and the other AA's are not heterocyclic. aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

M. Groups CCCXIII-CCCXXXVIII wherein n=4, $R=NR_1R_4$, at least one AA is a heterocyclic amino acid and M is as defined in Groups I-

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XXVI respectively,

N. Groups CCCXXXIX-CCCLXIV wherein n=4, R=NR_3R_4, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

O. Groups CCCXLV-CCCXC wherein n=4, R=NR_3R_4, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-XXVI respectively,

P. Groups CCCXCI-CMXVI wherein n=4, R=NR_3R_4, at least one AA is an acyclic amino acid and the other AA's are not heterocyclic, aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

Q. Groups CMXVII-CMXLII wherein n=1, R = -OH or an ester moiety, AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively,

R. Groups CMXLIII-CMLXVIII wherein n=1, R = -OH or an ester moiety, AA is an aromatic amino acid and M is as defined in Groups I-XXVI respectively,

S. Groups CMLXIX-CMXCIV wherein n=1, R = -OH or an ester moiety, AA is a cyclic amino acid and M is as defined in Groups I-XXVI respectively,

T. Groups CMXCV-MXX wherein n=1, R = -OH or an ester moiety, AA is an acyclic amino acid and M is as defined in Groups I-XXVI respectively,

U. Groups MXXI-MXLVI wherein n=2, R = -OH or an ester moiety,

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at least one AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively.

V. Groups MXLVII-MLXXII wherein n=2, R = -OH or an ester moiety, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

W. Groups MLXXIII-MXCVIII wherein n=2, R = -OH or an ester moiety, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-XXVI respectively,

X. Groups MXCIX-MCXXIV wherein n=2, R = -OH or an ester moiety, AA is an acyclic amino acid and the other AA is not heterocyclic, aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

Y. Groups MCXXV-MCL wherein n=3, R = -OH or an ester moiety, at least one AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively,

Z. Groups MCLI-MCLXXVI wherein n=3, R = -OH or an ester moiety, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

AA. Groups MCLXXVII-MCCII wherein n=3, R = -OH or an ester moiety, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-

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XXVI respectively,

BB. Groups MCCIII-MCCXXVIII wherein n=3, R = -OH or an ester moiety, at least one AA is an acyclic amino acid and the other AA's are not heterocyclic, aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

CC. Groups MCCXXIX-MCCLIV wherein n=4, R = -OH or an ester moiety, at least one AA is a heterocyclic amino acid and M is as defined in Groups I-XXVI respectively,

DD. Groups MCCLV-MCCLXXX wherein n=4, R = -OH or an ester moiety, at least one AA is an aromatic amino acid and the other AA's are not heterocyclic and M is as defined in Groups I-XXVI respectively,

EE. Groups MCCLXXXI-MCCCVI wherein n=4, R = -OH or an ester moiety, at least one AA is a cyclic amino acid and the other AA's are not heterocyclic or aromatic and M is as defined in Groups I-XXVI respectively,

FF. Groups MCCCVII-MCCCXXXII wherein n=4, R = -OH or an ester moiety, at least one AA is an acyclic amino acid and the other AA's are not heterocyclic, aromatic or cyclic and M is as defined in Groups I-XXVI respectively,

As set forth above, Group I is not the first appearing invention. The above order was used to set forth the distinct inventions in a systematic way and not in the order that the inventions appear in the claims. The first appearing invention in

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claim 1 would correspond to the compounds wherein n=2. R=NR_3R_4. at least one AA is an acyclic amino acid and the other AA's are not heterocyclic, aromatic or cyclic and M is hydrogen which are compounds falling with Group CLXXXIII. The international search has been established on this invention.